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No. 87-1194

IN THE
Supreme Court of the United States
OCTOBER TERM, 1987

THE COSMETIC, TOILETRY AND FRAGRANCE ASSOCIATION,
Petitioner,

v.

PUBLIC CITIZEN, *et al.*,
Respondents.

APPENDIX TO PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE DISTRICT OF COLUMBIA CIRCUIT

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APPENDIX A

UNITED STATES COURT OF APPEALS
FOR THE DISTRICT OF COLUMBIA CIRCUIT

No. 86-1548

PUBLIC CITIZEN, et al., PETITIONERS

v.

DR. FRANK YOUNG, COMMISSIONER,
FOOD AND DRUG ADMINISTRATION, et al., RESPONDENTS

COSMETIC, TOILETRY AND FRAGRANCE ASSOCIATION,
INTERVENOR

Petition for Review of an Order of the
Food and Drug Administration

No. 86-5150

PUBLIC CITIZEN, et al., APPELLANTS

v.

DEPARTMENT OF HEALTH & HUMAN SERVICES, et al.

Appeal from the United States District Court
for the District of Columbia

(Civil Action No. 85-00209)

Argued March 26, 1987

Decided October 23, 1987

William B. Schultz, with whom *Katherine A. Meyer* and *Alan B. Morrison* were on the brief for petitioner in No. 86-1548 and appellants in No. 86-5150.

Douglas N. Letter, Appellant Litigation Counsel, Department of Justice, with whom *Richard K. Willard*, Assistant Attorney General, *Robert L. Cynkar*, Deputy Assistant Attorney General, *Margaret A. Cotter*, Assistant Director, *Jacqueline H. Eagle*, Attorney, Department of Justice, *Thomas Scarlett*, Chief Counsel and *Richard E. Geyer*, Associate Chief Counsel, Food and Drug Administration were on the brief for respondents in No. 86-1548.

Robert C. Seldon, Assistant United States Attorney, with whom *Joseph E. diGenova*, United States Attorney, *Royce C. Lamberth*, *R. Craig Lawrence*, Assistant United States Attorneys, *Thomas Scarlett*, Chief Counsel and *Richard E. Geyer*, Associate Chief Counsel, Food and Drug Administration were on the brief for federal appellees in No. 86-5150.

John P. McKenna, with whom *Daniel R. Thompson* was on the brief for appellee, Certified Color Manufacturers Association in No. 86-5150.

Peter Barton Hutt for intervenor in No. 86-1548. *Robert M. Sussman* and *Bruce N. Kuhlik* were on the brief for the Cosmetic, Toiletry and Fragrance Association, appellee in No. 86-5150 and intervenor in No. 86-1548.

Before: RUTH B. GINSBURG and WILLIAMS, *Circuit Judges*, and HAROLD H. GREENE,* *District Judge*.

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* Of the United States District Court for the District of Columbia, sitting by designation pursuant to 28 U.S.C. § 292(a).

Opinion for the Court filed by *Circuit Judge* WILLIAMS.

WILLIAMS, *Circuit Judge*: The Color Additive Amendments of 1960, Pub. L. No. 86-618, 74 Stat. 397 (codified at 21 U.S.C. § 376 (1982)), part of the Food, Drug and Cosmetic Act (the "Act"), establish an elaborate system for regulation of color additives in the interests of safety. A color additive may be used only after the Food and Drug Administration ("FDA") has published a regulation listing the additive for such uses as are safe. Such listing may occur only if the color additive in question satisfies (among other things) the requirements of the applicable "Delaney Clause," § 706(b)(5)(B) of the Act, 21 U.S.C. § 376(b)(5)(B), one of three such clauses in the total system for regulation of color additives, food and animal food and drugs.[1] The Clause prohibits the listing of any color additive "found . . . to induce cancer in man or animal."

In No. 86-1548, Public Citizen and certain individuals challenge the decision of the FDA to list two color additives, Orange No. 17 and Red No. 19, based on quantitative risk assessments indicating that the cancer risks presented by these dyes were trivial. This case thus requires us to determine whether the Delaney Clause for color additives is subject to an implicit "*de minimis*" exception. We conclude, with some reluctance, that the Clause lacks such an exception.

In a second case argued the same day, No. 86-5150, Public Citizen and others challenged the FDA's persistence in giving "provisional" listing to ten color additives, including several found to cause cancer in labora-

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[1] The other clauses relate to food additives, 21 U.S.C. § 348(c)(3)(A), and to animal drugs, *id.* § 360b(d)(1)(H). All clauses prohibit carcinogens. The clauses differ slightly in language, more materially in statutory context and legislative history.

tory animals. The agency has since removed most of the colors at issue from the provisional list, mooting the case as to these colors. At present, only three of the original colors, Red Nos. 3, 33 and 36, are still provisionally listed. Apart from those rendered moot, we find that these claims are either foreclosed by circuit law or unripe.

I. The Delaney Clause and "de Minimis" Exceptions

A. *Factual Background*

The FDA listed Orange No. 17 and Red No. 19 for use in externally applied cosmetics on August 7, 1986. *See* 21 C.F.R. §§ 74.1267, 74.2267 (1987) (Orange No. 17); *id.* §§ 74.1319, 74.2319 (Red No. 19). In the listing notices, it carefully explained the testing processes for both dyes and praised the processes as "current state-of-the-art toxicological testing." 51 Fed. Reg. 28,331, 28,334 (Aug. 7, 1986) (Orange No. 17); *id.* at 28,346, 28,349 (Red No. 19). In both notices it specifically rejected industry arguments that the Delaney Clause did not apply because the tests were inappropriate for evaluation of the dyes. 51 Fed. Reg. at 28,342; *id.* at 28,358-59. It thus concluded that the studies established that the substances caused cancer in the test animals. *Id.* at 28,334-36, 28,341 (Orange No. 17 "induces cancer when tested in laboratory animals"); *id.* at 28,349-52, 28,357 (Red No. 19 "induces cancer when tested in laboratory animals").

The notices then went on to describe two quantitative risk assessments of the dyes, one by the Cosmetic, Toiletry and Fragrance Association ("CTFA," an intervenor here and the industry proponent of both dyes) and one by a special scientific review panel made up of Public Health Service scientists. Such assessments seek to define the extent of health effects of exposures to particular

hazards. As described by the National Research Council, they generally involve four steps: (1) hazard identification, or the determination of whether a substance is causally linked to a health effect; (2) dose-response assessment, or determination of the relation between exposure levels and health effects; (3) exposure assessment, or determination of human exposure; and (4) risk characterization, or description of the nature and magnitude of the risk. *See* National Research Council, *Risk Assessment in the Federal Government: Managing the Process* 3 (National Academy Press 1983) (*"Risk Assessment"*). All agree that gaps exist in the available information and that the risk estimator must use assumptions to fill those gaps. *See, e.g., Report of the Color Additive Scientific Review Panel* (Sept. 1985), Joint Appendix ("J.A.") in No. 86-1548, at 139-40, 167. The choice among possible assumptions is inevitably a matter of policy to some degree. *See Risk Assessment* at 3.[2]

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[2] Agencies have used quantitative risk assessments in a variety of regulatory contexts. For example, the Occupational Safety and Health Administration is under a mandate to establish standards "reasonably necessary or appropriate to provide safe or healthful . . . places of employment," 29 U.S.C. § 652(8) (1982), which was construed in *Industrial Union Dep't v. American Petroleum Institute,* 448 U.S. 607, 639-40 (1980), to call for promulgation of standards only where appropriate to remedy a "significant risk of material health impairment." In fulfillment of this mandate, OSHA used quantitative risk assessment in promulgating a rule on exposure limits to airborne inorganic arsenic. 48 Fed. Reg. 1864 (1983). *See also* Environmental Protection Agency, "Proposed Guidelines for Carcinogen Risk Assessment," 49 Fed. Reg. 46,294 (1984). The FDA itself has used the technique in evaluating safety where the Delaney Clause did not apply. *See* 47 Fed. Reg. 14,138 (1982) (Green No. 6). *See also* Cooper, *Stretching Delaney Till It Breaks,* Regulation 11 (Nov./Dec. 1985) (describing FDA's increasing confidence in quantitative risk assessment); Nichols and Zeckhauser, *The Perils of Prudence: How Conservative Risk Assessments Distort Regulation,* Regulation 13 (Nov./Dec. 1986) ("Quantitative risk assessment is an increasingly important tool in

The assessments considered the risk to humans from the substances when used in various cosmetics—lipsticks, face powders and rouges, hair cosmetics, nail products, bathwater products, and wash-off products. The scientific review panel found the lifetime cancer risks of the substances extremely small: for Orange No. 17, it calculated them as one in 19 billion at worst, and for Red No. 19 one in nine million at worst. The FDA explained that the panel had used conserative assumptions in deriving these figures, and it characterized the risks as "so trivial as to be effectively no risk." It concluded that the two dyes were safe. 51 Fed. Reg. at 28,344, 28,360.

The FDA candidly acknowledged that its safety findings represented a departure from past agency practice: "In the past, because the data and information show that D&C Orange No. 17 is a carcinogen when ingested by laboratory animals, FDA in all likelihood would have terminated the provisional listing and denied CTFA's petition for the externally applied uses . . . without any further discussion." *Id.* at 28,341; *accord id.* at 28,357 (same for Red No. 19). It also acknowledged that "[a] strictly literal application of the Delaney Clause would prohibit FDA from finding [both dyes] safe, and therefore, prohibit FDA from permanently listing [them]. . . ." *Id.* at 28,341; *id.* at 28,356. Because the risks presented by these dyes were so small, however, the agency declared that it had "inherent authority" under the *de minimis* doctrine to list them for use in spite of this language. *Id.* at 28,341; *id.* at 28,358. It indicated that as a general matter any risk lower than a one-in-one-

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regulatory decisions involving health and safety."). FDA has also used the technique in the face of the Delaney Clause in approving a carcinogenic food additive, methylene chloride. 50 Fed. Reg. 51,551 (1985). A challenge to the methylene chloride determination is currently pending before this court. *Public Citizen v. Bowen*, No. 86-1494.

million lifetime risk would meet the requirements for a *de minimis* exception to the Delaney Clause. *Id.* at 28,344; *id.* at 28,362.

Assuming that the quantitative risk assessments are accurate, as we do for these purposes, it seems altogther correct to characterize these risks as trivial. For example, CTFA notes that a consumer would run a one-in-a-million lifetime risk of cancer if he or she ate *one* peanut with the FDA-permitted level of aflatoxins once every *250* days (liver cancer). *See* J.A. 529, citing FDA Bureau of Foods, *Assessment of Estimated Risk Resulting From Aflatoxins in Consumer Peanut Products and Other Food Commodities* (1978). Another activity posing a one-in-a-million lifetime risk is spending 1,000 minutes (less than 17 hours) every year in the city of Denver—with its high elevation and cosmic radiation levels—rather than in the District of Columbia. *See* J.A. 530. Most of us would not regard these as high-risk activities. Those who indulge in them can hardly be thought of as living dangerously. Indeed, they are risks taken without a second thought by persons whose economic position allows them a broad range of choice.

According to the risk assessments here, the riskier dye poses one ninth as much risk as the peanut or Colorado hypothetical; the less risky one poses only one 19,000th as much.

It may help put the one-in-a-million lifetime risk in perspective to compare it with a concededly dangerous activity, in which millions nonetheless engage, cigarette smoking. Each one-in-a-million risk amounts to less than one *200,000th* the lifetime risk incurred by the average male smoker. J.A. 536, citing E. Crouch & R. Wilson, "Inter-Risk Comparisons," in J. Rodricks & R. Tardiff, eds., *Assessment and Management of Chemical Risks* 97, 105, 108 (1984). Thus, a person would have to be exposed to more than 2,000 chemicals bearing the one-in-

a-million lifetime risk, at the rates assumed in the risk assessment, in order to reach 100th the risk involved in smoking. To reach that level of risk with chemicals equivalent to the less risky dye (Orange No. 17), he would have to be exposed to more than 40 million such chemicals.

B. *Plain Language and the* de Minimis *Doctrine*

The Delaney Clause of the Color Additive Amendments provides as follows:

> a color additive . . . (ii) shall be deemed unsafe, and shall not be listed, for any use which will not result in ingestion of any part of such additive, if, after tests which are appropriate for the evaluation of the safety of additives for such use, or after other relevant exposure of man or animal to such additive, it is found by the Secretary to induce cancer in man or animal. . . .[3]

21 U.S.C. § 376(b)(5)(B).

The natural—almost inescapable—reading of this language is that if the Secretary finds the additive to "induce" cancer in animals, he must deny listing. Here, of course, the agency made precisely the finding that Orange No. 17 and Red No. 19 "induce[] cancer when tested in laboratory animals." (Below we address later agency pronouncements appearing to back away from these statements.)

The setting of the clause supports this strict reading. Adjacent to it is a section governing safety generally and directing the FDA to consider a variety of factors, including probable exposure, cumulative effects, and detection difficulties. 21 U.S.C. § 376(b)(5)(A). The contract in approach seems to us significant. For all safety

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[3] This quotation omits subsection (i), which concerns uses involving ingestion; none of the uses here at issue concerns such a use.

hazards other than carcinogens, Congress made safety the issue, and authorized the agency to pursue a multifaceted inquiry in arriving at an evaluation. For carcinogens, however, it framed the issue in the simple form, "If A [finding that cancer is induced in man or animals], then B [no listing]." There is language inviting administrative discretion, but it relates only to the process leading to the finding of carcinogenicity: "appropriate" tests or "other relevant exposure," and the agency's "evaluation" of such data. Once the finding is made, the dye "shall be deemed unsafe, and shall not be listed." 21 U.S.C. § 376(b)(5)(B).

Courts (and agencies) are not, of course, helpless slaves to literalism. One escape hatch, invoked by the government and CTFA here, is the *de minimis* doctrine, shorthand for *de minimis non curat lex* ("the law does not concern itself with trifles"). The doctrine—articulated in recent times in a series of decisions by Judge Leventhal—serves a number of purposes. One is to spare agency resources for more important matters. *See Alabama Power Co. v. Costle*, 636 F.2d 323, 360 (D.C. Cir. 1979). But that is a goal of dubious relevance here. The finding of trivial risk necessarily followed not only the elaborate animal testing, but also the quantitative risk assessment process itself; indeed, application of the doctrine required additional expenditure of agency resources.

More relevant is the concept that "notwithstanding the 'plain meaning' of a statute, a court must look beyond the words to the purpose of the act where its literal terms lead to 'absurd or futile results.'" *Alabama Power*, 636 F.2d at 360 n.89 (quoting *United States v. American Trucking Ass'ns*, 310 U.S. 534, 543 (1939)). Imposition of pointless burdens on regulated entities is obviously to be avoided if possible, *see Alabama Power*, 636 F.2d at 360-61, especially as burdens on them almost invariably entail losses for their customers: here, obviously, loss of

access to the colors made possible by a broad range of dyes.

We have employed the concept in construing the Clean Air Act's mandate to the Environmental Protection Agency to set standards providing "an ample margin of safety to protect the public health," 42 U.S.C. § 7412(b)(1) (1982). That does not, we said, require limits assuring a "risk-free" environment. Rather, the agency must decide "what risks are acceptable in the world in which we live" and set limits accordingly. *See Natural Resources Defense Council, Inc. v. EPA*, 824 F.2d 1146, 1164-65 (D.C. Cir. 1987) (citing *Industrial Union Dep't, AFL-CIO v. American Petroleum Inst.*, 448 U.S. 607, 642 (1980). Assuming as always the validity of the risk assessments, we believe that the risks posed by the two dyes would have to be characterized as "acceptable." Accordingly, if the statute were to permit a *de minimis* exception, this would appear to be a case for its application.[4]

Moreover, failure to employ a *de minimis* doctrine may lead to regulation that not only is "absurd or futile" in some general cost-benefit sense but also is directly contrary to the *primary* legislative goal. *See id.* at 360 (*de minimis* doctrine a "tool to be used in implementing the legislative design"). In a certain sense, precisely that may be the effect here. The primary goal of the Act is human safety, but literal application of the Delaney Clause may in some instances increase risk. No one contends that the Color Additive Amendments impose a zero-

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[4] We do not, of course, purport to decide the appropriate dividing point between *de minimis* and other risks. FDA's proposed one-in-one-million dividing point has been used by EPA to distinguish acceptable and unacceptable risks. 49 Fed. Reg. 46,294 (1984) (general guidelines); 51 Fed. Reg. 1602, 1635 (1986) (hazardous wastes). FDA has used the same break point to determine whether the general safety clause of the Act applies. 47 Fed. Reg. 14,138 (1982).

risk standard for non-carcinogenic substances; if they did, the number of dyes passing muster might prove miniscule. As a result, makers of drugs and cosmetics who are barred from using a carcinogenic dye carrying a one-in-20-million lifetime risk may use instead a non-carcinogenic, but toxic, dye carrying, say, a one-in-10-million lifetime risk. The substitution appears to be a clear loss for safety.

Judge Leventhal articulated the standard for application of *de minimis* as virtually a presumption in its favor: "Unless Congress has been extraordinarily rigid, there is likely a basis for an implication of *de minimis* authority to provide [an] exemption when the burdens of regulation yield a gain of trivial or no value." *Alabama Power*, 636 F.2d at 360-61. But the doctrine obviously is not available to thwart a statutory command; it must be interpreted with a view to "implementing the legislative design." *Id.* at 360. Nor is an agency to apply it on a finding merely that regulatory costs exceed regulatory benefits. *Id.* at 361.

Here, we cannot find that exemption of exceedingly small (but measurable) risks tends to implement the legislative design of the color additive Delaney Clause. The language itself is rigid; the context—an alternative design admitting administrative discretion for all risks other than carcinogens—tends to confirm that rigidity. Below we consider first the legislative history; rather than offering any hint of softening, this only strengthens the inference. Second, we consider a number of factors that make Congress's apparent decision at least a comprehensible policy choice.

1. *Legislative History*

The Delaney Clause arose in the House bill and was, indeed, what principally distinguished the House from the Senate bill. The House included it in H.R. 7624, 106 Cong. Rec. 14,353-56, and the Senate accepted the lan-

guage without debate, 106 Cong. Rec. 15,133 (1960). The House committee gave considerable attention to the degree of discretion permitted under the provision. The discussion points powerfully against any *de minimis* exception, and is not contradicted either by consideration on the House floor or by a post-enactment colloquy in the Senate.

House Committee. The House Report on the Color Additive Amendments is the most detailed evidence as to Congress's intentions on this issue. H.R. Rep. No. 1761, 86th Cong., 2d Sess. (1960) (hereinafter the "*House Report*"). In discussing the Clause, the report first explains the source of concern: "[T]oday cancer is second only to heart disease as a cause of death among the American people. Every year, approximately 250,000 people die of cancer in this country. Approximately 450,000 new cases of cancer are discovered each year." *Id.* at 11. The report reflects intense congressional concern over cancer risks from man-made substances.[5]

The report acknowledged the "many unknowns about cancer," but highlighted certain areas of general agreement: "Laboratory experiments have shown that a number of substances when added to the diet of test animals have produced cancers of various kinds in the test animals. It is this fact—namely, that small quantities of certain materials over a period of time will cause abnormal cell growth in animals—that gave rise to the Delaney anticancer clause. . . ." *Id.* The report quoted at length from the hearing testimony of Arthur S. Flemming, Secretary of Health, Education, and Welfare (the parent agency of the FDA and the predecessor of Health and Human Services). The Secretary took a very strong line on the absence of a basis for finding "threshold" levels below which carcinogens would not be dangerous:

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[5] For other indicia of congressional anxiety, *see infra* pp. 19-20 and nn.11-12.

> We have no basis for asking Congress to give us discretion to establish a safe tolerance for a substance which definitely has been shown to produce cancer when added to the diet of test animals. We simply have no basis on which such discretion could be exercised because no one can tell us with any assurance at all how to establish a safe dose of any cancer-producing substance.

Id. at 13.[6]

Secretary Flemming also developed the theme that, with many cancer risks inescapably present in the environment, it made sense to remove unnecessary ones:

> Unless and until there is a sound scientific basis for the establishment of tolerances for carcinogens, I believe the Government has a duty to make clear—in law as well as in administrative policy—that it will do everything possible to put persons in a position where they will not unnecessarily be adding residues of carcinogens to their diet.
>
> The population is inadvertently exposed to certain carcinogens. . . . In view of these facts, it becomes all the more imperative to protect the public from deliberate introduction of additional carcinogenic materials into the human environment.
>
> . . .

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[6] In fact the existence of a threshold for chemical carcinogens, below which their use would have no ill effect, appears to depend on whether one is speaking of an "initiating" agent, a "promoting" agent, or a "complete carcinogen." (The latter both initiates and promotes.) Both activities are necessary for the production of tumors. Both the theory of the operation of initiating agents and the empirical data support the belief that for them no threshold applies. Equally, the theory and data as to promoting agents support the view that there is a "no-effect" threshold level. *See* H. Pitot, "Principles of Cancer Biology: Chemical Carcinogenesis," 1 *Cancer: Principles and Practice of Oncology* 79-99 (V. DeVita, S. Hellman, & S. Rosenberg, 2d ed. 1985).

> It is clear that if we include in our diet substances that induce cancer when included in the diet of test animals, we are taking a risk. In light of the rising number of cases of cancer, why should we take that risk?

Id. at 12-13.

Before adopting Flemming's no-threshold premise the House committee heard many witnesses on the opposite side of the debate,[7] and its *Report* acknowledges their contentions. *Id.* at 13 (witnesses stated that it was "possible to establish safe tolerance levels"). It also notes that some took the position that the ban should "apply only to colors that induce cancer when ingested in an amount and under conditions reasonably related to their

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[7] *See* Color Additives: Hearings Before the House Comm. on Interstate and Foreign Commerce, 86th Cong., 2d Sess. 115-18 (1960) [hereinafter *Color Additives Hearings*] (testimony of representative of the Toilet Goods Association) (arguing that risk from ingestion of lipstick colors did not justify absolute prohibition and proposing amendment specifying that tests should be "appropriate" to proposed uses of additive for which listing was sought); *id.* at 224 (paper submitted by Edward J. Matson of Abbott Laboratories) ("One thing already accepted by most experts in the field is that there truly is a threshold dose of a carcinogen, below which cancer is not produced in animals . . . [W]e cannot yet predict the threshold dose in man from knowledge of the threshold dose in experimental animals."); *id.* at 237-38 (representative of Manufacturing Chemists Association) ("there is lack of agreement among scientists as to whether a safe level can be set for all carcinogens"); *id.* at 260-61 (statement of representative of Pharmaceutical Manufacturers) ("when you consider conditions reasonably related to the intended use, I understand there is adequate scientific knowledge as to whether [an additive] could be used safely or not"); *id.* at 318 (representative of Pharmaceutical Manufacturers Association) (arguing that "as a practical matter, no-effect levels of carcinogens must be recognized" because "[w]e cannot dispense with the many common foods which are implicated in carcinogenicity").

intended use." *Id.*[8] Similarly, it notes support for making carcinogenicity simply one of the factors for the Secretary to consider in determining safety. *Id.*[9] Finally, it mentions a position taken by some scientific witnesses strikingly similar to that taken by FDA here. These experts suggested that, in spite of the difficulties in designing and evaluating tests for carcinogenicity, the Secretary "should have the authority to decide that a minute amount of a cancer-producing chemical may be added to man's food after a group of scientists consider all the facts and conclude that the quantity to be tolerated is probably without hazard." *Id.* at 13-14.[10]

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[8] For testimony advocating such a position, *see Color Additives Hearings* at 118, 224, 313; *see also id.* at 396 (Report of the Panel on Food Additives of the President's Scientific Advisory Committee) [hereinafter "Kistiakowsky Report"] ("dietary levels of carcinogenic agents exist at which the probability of cancer induction in animals is near zero").

[9] Several industry representatives and other experts testified that the Delaney Clause was too inflexible as written and should be modified to permit greater administrative discretion. *See Color Additives Hearings* at 140-42 (testimony of representative of the Certified Color Industry Committee) (characterizing the provision as "an unwise, absolute rigid standard" and as lacking "any flexibility for future action" and proposing language to make carcinogenicity one of the factors considered in the general safety determination); *id.* at 237-38 (representative of Manufacturing Chemists Association) (arguing that requiring "the Secretary to return to Congress when a scientific breakthrough occurs injects inflexibility . . . ." and anticipating problems such inflexibility could cause); *id.* at 266 (vice president of Eli Lilly & Co.) ("The main objection to the Delaney amendment is its rigidity."); *cf. id.* at 397 (Kistiakowsky Report states that "the panel believes that the probability of cancer induction from a particular carcinogen in minute doses may be eventually assessed by weighing scientific evidence as it becomes available").

[10] *See Color Additives Hearings* at 429 (statement of Dr. Charles J. Kensler); *see also id.* at 468 (statement of Dr. William J. Darby) (favoring omission of Delaney Clause as

The committee rejected all these positions on the grounds that they would "weaken the present anticancer clause." *Id.* at 13. The report responded to them with another quote from Secretary Flemming's hearing testimony, reflecting the view that agency discretion should cease once "a substance has been shown to produce cancer when added to the diet of test animals":

> The rallying point against the anticancer provision is the catch phrase that it takes away the scientists's [sic] right to exercise judgment. The issue thus made is a false one, because the clause allows the exercise of all the judgment that can safely be exercised on the basis of our present knowledge. . . . It allows the Department and its scientific people full discretion and judgment in deciding whether a substance has been shown to produce cancer when added to the diet of test animals. But once this decision is made, the limits of judgment have been reached and there is no reliable basis on which discretion could be exercised in determining a safe threshold dose for the established carcinogen.

Id. at 14.

Beyond this delineation of the intended scope of discretion, the *House Report* also addressed the possibility that its scientific premise—the absence of a threshold—might prove false. Its evident solution was that *Congress*, not the FDA, should examine the evidence and find a solution. The *House Report* at 12 quotes Secretary Flemming to precisely this effect:

> Whenever a sound scientific basis is developed for the establishment of tolerances for carcinogens, we will request the Congress to give us that authority. We believe, however, that the issue is so important that

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long as there is "a law providing this adequate protection combined with ample provision for scientific review and judgment, plus publication of the basis of decisions").

> the elected representatives of the people should have the opportunity of examining the evidence and determining whether or not the authority should be granted.

See also Color Additives Hearings at 34 (administration statement that "if additional scientific evidence indicates that further relaxation of the Delaney amendment is desirable, it will of course be proposed").

The government and CFTA note that exempting substances shown by quantitative risk assessment to carry only trivial risks rests on a quite different foundation from establishing threshold levels below which no cancer is thought to occur. We agree that the two are distinguishable, but do not find the distinctions between them to cut in favor of a *de minimis* exception. If it is correct to read the statute as barring tolerances based on an assumed threshold, it follows *a fortiori* that the agency must ban color additives with real but negligible cancer risks.

House floor. In the House debate, little of substance occurred. Congressman Delaney contended that the anticancer provision was essential "if the public health is to be adequately protected," 106 Cong. Rec. at 14,350, and asserted in conclusory terms the inability to establish a safe dose or tolerance, *id.* Congressman Rogers, describing the anticancer clause (which he supported), observed that "[t]he 'safe for use' principle does not apply to situations where carcinogenicity is at issue." *Id.* at 14,371. One participant, Congressman Allen, expressed the view that the anticancer clause was "unnecessary and restrictive," and that the "decision on safety [should] be determined by the Secretary of Health, Education and Welfare rather than . . . determined by law." *Id.* at 14,351. Accordingly, he urged passage of the Senate bill instead. Although Congressman Allen's view of the bill was negative, his interpretation seems to accord with

that of its proponents: a ban follows automatically from a finding of carcinogenicity in man or animal.

Post-enactment Senate colloquy. The inferences of rigidity supported by the above remarks are drawn slightly in question—but ultimately, we think, not much—by an exchange that occurred the day *after* the Senate took final action on the final version of the Act. Senator Javits politely complained about the Senate's acting on this legislation in his absence. He secured unanimous consent for including in the Record the conclusions of a then-recent Report of the Panel on Food Additives of the President's Advisory Committee (the "Kistiakowsky Report"). He characterized the Report as stating that "authority such as that conferred by the amendment [the Report was addressed to the food additive Delaney Clause] should be used and applied within the 'rule of reason.'" 106 Cong. Rec. at 15,381. After Senators Dirksen and Hill assented to this proposition, Javits agreed to lay on the table a motion to reconsider the vote of the previous day. *Id.*

Appellees interpret the rule-of-reason colloquy as squarely supporting their *de minimis* approach, but in fact it is ambiguous. The Kistiakowsky Report defined "rule of reason" by a quotation from *Rathbun v. United States*, 355 U.S. 107, 109 (1957): "Every statute must be interpreted in the light of reason and common understanding to reach the results intended by the legislature." The proposition accords exactly with the way in which Judge Leventhal formulated the test for application of the *de minimis* doctrine: would the doctrine "implement[] the legislative design"? *Alabama Power*, 636 F.2d at 360. But that is the question, not the answer. Thus the exchange invoking the rule of reason appears to do no more than exhort us to pursue the inquiry we've been pursuing.

Indeed, although the Kistiakowsky Report itself points out some possible consequences of "a literal interpreta-

tion" of the food additive Delaney Clause, *see Color Additives Hearings* at 396-97, and states that in its interpretation the FDA "must employ the 'rule of reason' " as defined in *Rathbun*, *id.* at 398, it also acknowledges that clause may prevent the agency from "exercis[ing] discretion consistent with the recommendations of this report," *id.* Thus a commitment to the "rule of reason" in this context hardly carries an inexorable implication that the color additive Delaney Clause grants the FDA the discretion it now claims.

Taken as a whole, the remarks do not seem strong enough to undermine the inference we have drawn that the clause was to operate automatically once the FDA squeezed the scientific trigger. This is so even without regard to the usual hazards of post-enactment legislative history, which ordinarily lead to its being disregarded altogether. *See Regional Rail Reorganization Act Cases*, 419 U.S. 102, 132 (1974) ("post-passage remarks of legislators, however explicit, cannot serve to change the legislative intent of Congress expressed before the Act's passage").

2. *Possible Explanations for an Absolute Rule*

Like all legislative history, this is hardly conclusive. But short of an explicit declaration in the statute barring use of a *de minimis* exception, this is perhaps as strong as it is likely to get. Facing the explicit claim that the Clause was "extraordinarily rigid," a claim well supported by the Clause's language in contrast with the bill's grants of discretion elsewhere, Congress persevered.

Moreover, our reading of the legislative history suggests some possible explanations for Congress's apparent rigidity. One is that Congress, and the nation in general (at least as perceived by Congress), appear to have been truly alarmed about the risks of cancer. *House Report* at 11; *Color Additive Hearings* at 327 (statement of

Rep. Oren Harris, Chairman); *id.* at 491 (statement of Dr. Zavon) (Delaney Clause "tends to highlight the current hysteria regarding cancer"). This concern resulted in a close focus on substances increasing cancer threats and a willingness to take extreme steps to lessen even small risks.[11] Congress hoped to reduce the incidence of cancer by banning carcinogenic dyes, and may also have hoped to lessen public fears by demonstrating strong resolve.[12]

A second possible explanation for Congress's failure to authorize greater administrative discretion is that it perceived color additives as lacking any great value. For example, Congressman Delaney remarked, "Some food additives serve a useful purpose. . . . However, color additives provide no nutrient value. They have no value at all, except so-called eye appeal." *Color Additives Hearings* at 108. Representative Sullivan said, "we like the bright and light [lipstick] shades but if they cannot safely be produced, then we prefer to do without these particular shades." *Id.* at 114. And Representative King: "The colors which go into our foods and cosmetics are in no way essential to the public interest or the national security. . . . [C]onsumers will easily get along without [carcinogenic colors]." *Id.* at 246-47.

It is true that the legislation as a whole implicitly recognizes that color additives are of value, since one of

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[11] *See Color Additives Hearings* at 341 (testimony of representative of Consumers Union) ("we are faced with an epidemic, an epidemic of cancer, a chronic disease, and . . . all measures that will protect the public health should be taken, even at the cost of discomfort or sacrifice, financial sacrifice, to some segments of industry.").

[12] *Color Additive Hearings* at 327 (statement of Rep. Harris) (noting that "almost everyone[] is so conscious of cancer as a dread disease" and hypothesizing that throwing out the Delaney Clause "would create so much fear in the mind of the American people" that they might react against industry).

its purposes was to allow tolerances for certain dyes—harmful but not carcinogenic—that would have been banned under the former law. *See House Report* at 8-9; S. Rep. No. 795, 86th Cong., 1st Sess. 1-2 (1959). There was also testimony pointing out that in some uses color additives advance health: they can help identify medications and prevent misapplications where a patient must take several. *See Color Additives Hearings* at 255 (statement of representative of Pharmaceutical Manufacturers Association). Nevertheless, there is evidence that Congress thought the public could get along without carcinogenic colors, especially in view of the existence of safer substitutes. Thus the legislators may have estimated the costs of an overly protective rule as trivial.

So far as we can determine, no one drew the legislators' attention to the way in which the Delaney Clause, interacting with the flexible standard for determining safety of non-carcinogens, might cause manufacturers to substitute more dangerous toxic chemicals for less dangerous carcinogens. *See* discussion at [10] *supra*. But the obviously more stringent standard for carcinogens may rest on a view that cancer deaths are in some way more to be feared than others.

Finally, as we have already noted, the House committee (or its amanuenses) considered the possibility that its no-threshold assumption might prove false and contemplated a solution: renewed consideration by Congress.

Considering these circumstances—great concern over a specific health risk, the apparently low cost of protection, and the possibility of remedying any mistakes—Congress's enactment of an absolute rule seems less surprising.

C. *Special Arguments for Application of de Minimis*

Apart from their contentions on legislative history, the FDA and CTFA assert two grounds for a *de minimis* exception: an analysis of two cases applying *de minimis*

concepts in the food and drug regulation context, and contentions that, because of scientific advances since enactment, the disallowance of *de minimis* authority would have preposterous results in related areas of food and drug law. (We treat an argument based on a new interpretation of the statutory language separately in section I-D.) We are, ultimately, not persuaded.

1. De minimis *cases*

Monsanto Co. v. Kennedy, 613 F.2d 947 (D.C. Cir. 1979) (Leventhal, J.), considered whether acrylonitrile in beverage containers was a "food additive" within the meaning of the Food, Drug and Cosmetic Act's definition of that term:

> any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food . . . if such substance is not generally recognized . . . to be safe under the conditions of its intended use . . .

Section 201(s), Food, Drug and Cosmetic Act, 21 U.S.C. § 321(s) (1982).

By operation of the second law of thermodynamics, any substance, obviously including acrylonitrile, will migrate in minute amounts from a bottle into a beverage within the bottle. Questions had been raised about its safety. The court found the FDA's decision to ban its use insufficiently well considered. In remanding the case for reconsideration, the court emphasized the FDA Commissioner's discretion to exclude a chemical from the statutory definition of food additives if "the level of migration into food . . . is so negligible as to present no public health or safety concerns." *Id.* at 955.

The opinion makes no suggestion that anyone supposed acrylonitrile to be carcinogenic, or that the Delaney Clause governing food additives, 21 U.S.C. § 348(c)(3)(A),

was in any way implicated. Thus the case cannot support a view that the food additive Delaney Clause (or, obviously, the color additive one) admits of a *de minimis* exception.[13]

Scott v. Food and Drug Administration, 728 F.2d 322 (6th Cir. 1984) (*per curiam*), involves the color additive Delaney Clause, but is nonetheless distinguishable. Petitioner challenged the FDA's listing of Green No. 5, on the grounds that it contained a chemical impurity in minute quantities that had been found to cause cancer in test animals. The dye as a whole, however, had been found not to induce cancer in test animals. *See* 47 Fed. Reg. 49,628, 49,629 (1984). The Sixth Circuit upheld the FDA's decision that the Delaney Clause of the Color Additive Amendments did not apply. The court cited *Monsanto* in support of upholding the FDA's view that it had discretion "to find that low-level migration into food of substances in *indirect* additives is so insignificant as to present no public health or safety concerns." *Id.* at 325 (quoting the FDA's statement of its own discretion) (emphasis added).

We must evaluate *Scott* in light of the possibility that the carcinogenic impurity in question acted as an "initiating agent" or was a "complete carcinogen," *see* note 6 *supra*, and, accordingly, would be subject to no threshold. If so, it would seem that if the impurity itself were carcinogenic, so would be any substance to which it was added.

Application of a *de minimis* exception for *constituents* of a color additive, however, seems to us materially different from use of such a doctrine for the color additive itself. As the *Scott* court noted, the FDA's action was completely consistent with the plain language of the stat-

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[13] As we note below, the operation of the food additive Delaney Clause raises complex issues distinct from those of this appeal.

ute, as there was no finding that the *dye* caused cancer in animals. 728 F.2d at 325. Here, as we have observed, application of a *de minimis* exception requires putting a gloss on the statute qualifying its literal terms.

Monsanto and *Scott* demonstrate that the *de minimis* doctrine is alive and well in the food and drug context, even on the periphery of the Delaney Clauses. But no case has applied it to limit the apparent meaning of any of those Clauses in their core operation.

2. *Scientific Advance and the Implications for Food Additive Regulation*

The CTFA also argues that in a number of respects scientific advance has rendered obsolete any inference of congressional insistence on rigidity. CTFA notes that while in 1958 (date of enactment of the food additive Delaney Clause) there were only four known human carcinogens, by 1978 there were 37 substances known to produce cancer in humans and over 500 in animals. They identify an impressive array of food ingredients now found to be animal carcinogens and that appear in a large number of food products. These include many items normally viewed as essential ingredients in a healthy diet, such as vitamins C and D, calcium, protein, and amino acids. If the color additive Delaney Clause has no *de minimis* exception, it follows (they suggest) that the food additive one must be equally rigid. The upshot would be to deny the American people access to a healthy food supply.

As a historical matter, the argument is overdrawn: the House committee was clearly on notice that certain common foods and nutrients were suspected carcinogens.[14]

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[14] *See Color Additives Hearings* at 270 (statement of vice-president of Eli Lilly) (noting substances implicated in carcinogenicity in animals, including coffee, tea, milk, cream, cocoa, claret, caffeine, whiskey, sulfonamides, fat, cholesterol,

Beyond that, it is not clear that an interpretation of the food additive Delaney Clause identical with our interpretation of the color additive clause would entail the feared consequences. The food additive *definition* contains an exception for substances "generally recognized" as safe (known as the "GRAS" exception),[15] an exception that has no parallel in the color additive definition, 21 U.S.C. § 321(t)(1). That definition may permit a *de minimis* exception at a stage that logically precedes the FDA's ever reaching the food additive Delaney Clause. Indeed, *Monsanto* so holds—though, as we have noted, in a case not trenching upon the food additive Delaney Clause. Moreover, the GRAS exception itself builds in special protection for substances used in food

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vitamins, eggs, sugars, and others); *id.* at 318, 328 (testimony of Representative of Pharmaceutical Manufacturers' Association) ("so many of our common foods do contain carcinogens"); *id.* at 337-38 (testimony of representative of Consumers' Union) ("the fact that weak carcinogens are present in natural foods is no justification" for tolerances for carcinogenic additives); *id.* at 342 (statement of Rep. Nelson) ("we have been told that, for example, hens' eggs, milk, beef, soybeans, corn, lettuce alfalfa, have certain factors in them that create cancer"); *id.* at 397 (Kistiakowsky Report) ("In foodstuffs, as they occur in nature, one finds traces of chemicals which in larger amounts are generally accepted as carcinogenic . . . ."); *id.* at 427 (Rep. Flynt) (asking witness whether it was "substantially true that nearly every element of food known at the present time if either injected or ingested in large quantities is capable of producing cancer first or toxicity secondly?").

[15] The pertinent part of 21 U.S.C. § 321(s) excepts a substance

> generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case as a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use . . . .

prior to January 1, 1958, which may be shown to be safe "through either scientific procedures or experience based on common use in food." Indeed, the Kistiakowsky Report, filed with the House committee, stated that the grandfathering provision of the food additives Delaney Clause "considerably narrows [its] effect . . . on industry and the public." *See Color Additives Hearings* at 395.

The relationship of the GRAS exception and the food additive Delaney Clause clearly poses a problem: if the food additive definition allows the FDA to classify as GRAS substances carrying trivial risks (as *Monsanto* and our recent decision in *Natural Resources Defense Council v. EPA* seem to suggest), but the food additive Delaney Clause is absolute, then Congress has adopted inconsistent provisions. *Cf. Color Additives Hearings* at 313 (representative of Pharmaceutical Manufacturers Association testifies that Secretary Flemming will propose legislation to delete the grandfathering provision from the food additives definition because of inconsistency with the food additives Delaney Clause). On the other hand, if (1) the GRAS exception does not encompass substances with trivial carcinogenic effect (especially if its special provision for substances used before 1958 does not do so for long-established substances), and (2) the food additive Delaney Clause is as rigid as we find the color additive clause to be, conceivably the consequences identified by the CTFA, or some of them, may follow. All these are difficult questions, but they are neither before us nor is their answer foreordained by our decision here.

Moreover, we deal here only with the color additive Delaney Clause, not the one for food additives. Although the clauses have almost identical wording, the context is clearly different. Without having canvassed the legislative history of the food additive Delaney Clause, we may

safely say that its proponents could not have regarded as trivial the social cost of banning those parts of the American diet that CTFA argues are at risk.

Finally, even a court decision construing the food additive provisions to require a ban on dietary essentials would not, in fact, bring about such a ban. As Secretary Flemming noted, in words selected by the *House Report* for quotation, the FDA could bring critical new discoveries to Congress's attention. If the present law would lead to the consequences predicted, we suppose that the FDA would do so, and that Congress would respond.

D. *The Meaning of "[I]nduce Cancer"*

After Public Citizen initiated the litigation in No. 86-5150, the FDA published a notice embellishing the preamble to its initial safety determinations. 52 Fed. Reg. at 5081 (Orange No. 17); *id.* at 5083 (Red No. 19). These notices effectively apply quantitative risk assessment at the stage of determining whether a substance "induce[s] cancer in man or animal." They assert that even where a substance does cause cancer in animals in the conventional sense of the term, the FDA may find that it does not "induce cancer in man or animal" within the meaning of 21 U.S.C. § 376(b)(5)(B). It is not crystal clear whether such a negative finding would flow simply from a quantitative risk assessment finding the risk to be trivial for humans under conditions of intended use, or whether it would require a projection back to the laboratory animals: *i.e.*, an assessment that the risk would be trivial for animals exposed to the substance in quantities proportional to the exposure hypothesized for human risk assessment purposes. (Perhaps the distinction is without a difference.) In any event, the notices argued:

> The words "induce cancer in man or animal" as used in the Delaney Clause are terms of art intended to convey a regulatory judgment that is something more

> than a scientific observation that an additive is carcinogenic in laboratory animals. To limit this judgment to such a simple observation would be to arbitrarily exclude from FDA's consideration developing sophisticated testing and analytical methodologies, leaving FDA with only the most primitive techniques for its use in this important endeavor to protect public health. Certainly the language of the Delaney Clause itself cannot be read to mandate such a counterproductive limit on FDA's discharge of its responsibilities.

Id. at 5082; *id.* at 5084.

The notices acknowledged that the words "to induce cancer" had not been "rigorously and unambiguously" so limited in the previous notices. *Id.* at 5082; *id.* at 5084. This is a considerable understatement. The original determinations were quite unambiguous in concluding that the colors induced cancer in animals in valid tests; the explanations went to some trouble to rebut industry arguments to the contrary. Despite these arguments, FDA concluded that the tests demonstrated that the dyes were responsible for increases in animal tumors.

The plain language of the Delaney Clause covers all animals exposed to color additives, including laboratory animals exposed to high doses. It would be surprising if it did not. High-dose exposures are standard testing procedure, today just as in 1960; such high doses are justified to offset practical limitations on such tests: compared to expected exposure of millions of humans over long periods, the time periods are short and the animals few.[16] Many references in the legislative history reflect

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[16] *See, e.g.*, Office of Science and Technology Policy, "Chemical Carcinogens; Review of the Science and Its Associated Principles," 49 Fed. Reg. 21,594, 21,598 (1984) ("It is appropriate to use test doses that generally exceed human exposure levels in order to overcome the inherent insensitivity of the traditional design of the long-term animal test.").

awareness of reliance on animal testing,[17] and at least the more sophisticated participants must have been aware that this meant high-dose testing. A few so specified.[18]

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[17] *See House Report* at 11 (explaining the Delaney Clause's foundation in experiments showing that "a number of substances when added to the diet of test animals have produced cancers of various kinds in the test animals"); *Color Additives Hearings* at 46-47, 50-55 (summary of National Cancer Institute study describing animal testing techniques and describing uncertainties in predicting human responses from animal tests); *id.* at 74 (testimony of Secretary of HEW Flemming) ("anticancer clause constitutes sound public policy in view of the fact that no one knows how much or how little of a substance will induce cancer when added to the diet of man if it has been demonstrated that it will induce cancer when added to the diet of a test animal"); *id.* at 396 (Kistiakowsky Report) ("*Definition of induced cancer in animals.* . . . The criteria for defining whether or not a 'cancer' has been induced in experimental animals are varied."); *id.* at 424 (remark of Rep. Dingell); *id.* at 514 (testimony of Sec. Flemming) ("where those tests show that a substance will induce cancer when included in the diet of a test animal, . . . it will be banned."); 106 Cong. Rec. 14,350 (1960) (remarks of Rep. Delaney) ("a number of these dyes have been shown to induce cancer in experimental animals, and are strongly suspected as being able to induce cancer in man."); *id.* at 14,372 (remarks of Rep. Rogers) ("the point was made by scientific experts that many substances when administered to laboratory animals in certain quantities and under certain conditions are capable of inducing cancer.").

[18] *See* 106 Cong. Rec. 14,372 (remarks of Rep. Kyl) (expressing reservations about Delaney Clause and stating "[t]he prohibition is based on the assumption that a substance which increases the incidence of cancer when included in the diet of animals at any dose may increase the incidence of cancer in man."); *Color Additive Hearings* at 396 (Kistiakowsky Report) (notes that food additive Delaney Clause prohibition "is based on the assumption that a substance which increases the incidence of cancer when included in the diet of animals at any dose level may increase the incidence of cancer when included in the diet of man even when present in amounts detectable only by the most sensitive analytical techniques.").

All this indicates to us that Congress did not intend the FDA to be able to take a finding that a substance causes only trivial risk in humans and work back from that to a finding that the substance does not "induce cancer in . . . animals." This is simply the basic question—is the operation of the clause automatic once the FDA makes a finding of carcinogenicity in animals?—in a new guise. The only new argument offered in the notices is that, without the new interpretation, only "primitive techniques" could be used. In fact, of course, the agency is clearly free to incorporate the latest breakthroughs in animal testing; indeed, here it touted the most recent animal tests as "state of the art." The limitation on techniques is only that the agency may not, once a color additive is found to induce cancer in test animals in the conventional sense of the term, undercut the statutory consequence. As we find the FDA's construction "contrary to clear congressional intent," *Chevron U.S.A. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837, 843 n.9 (1984), we need not defer to it.

* * *

In sum, we hold that the Delaney Clause of the Color Additive Amendments does not contain an implicit *de minimis* exception for carcinogenic dyes with trivial risks to humans. We based this decision on our understanding that Congress adopted an "extraordinarily rigid" position, denying the FDA authority to list a dye once it found it to "induce cancer in . . . animals" in the conventional sense of the term. We believe that, in the color additive context, Congress intended that if this rule produced unexpected or undesirable consequences, the agency should come to it for relief. That moment may well have arrived, but we cannot provide the desired escape.

II. Provisional Listing

The regulatory scheme of the Color Additive Amendments included grandfathering provisions for commer-

cially established color additives. Pub. L. 86-618, tit. II, § 203, 74 Stat. 404 (uncodified provisions appearing at 21 U.S.C. § 376 note (1982)). These allowed provisional listing of established dyes pending testing for a two-and-a-half year period. They empowered the Secretary to extend the listing

> "for such period or periods as he finds necessary to carry out the purpose of this section, if in the Secretary's judgment such action is consistent with the objective of carrying to completion in good faith, as soon as reasonably practicable, the scientific investigations necessary for making a determination as to listing such additive. . . ."

Id. § 203(a)(2).

The process of completing these scientific investigations is only now being completed. When the litigation in No. 86-5150 began, ten color additives were on the provisional list. *Public Citizen v. Department of Health and Human Services*, No. 85-1573 (D.D.C. Feb. 13, 1986). Today, only three—Red No. 3, Red No. 33, and Red No. 36—remain.

Public Citizen petitioned for a ban on the provisionally listed colors; when the petition was denied, it sued in the court below. The court granted summary judgment for the FDA (and other appellees supporting provisional listing).

In *McIlwain v. Hayes*, 690 F.2d 1041 (D.C. Cir. 1982), this court set forth the guidelines governing challenges to the speediness of the Secretary's evaluations of provisionally listed dyes. The *McIlwain* court determined that agency discretion to postpone the expiration of provisional listings was limited only as follows: "Such postponements must be consistent with the public health, and the Commissioner must judge that the scientific investigations are going forward in good faith and will be completed as soon as reasonably practicable." *Id.* at 1047.

The majority acknowledged that it was doubtful that Congress foresaw the advances in testing technology that occasioned the delays, but saw no reason to depart from the statute's plain language. *Id.*

McIlwain controls here. The FDA has found that the postponements for further evaluation of Red No. 3, Red No. 33, and Red No. 36 are consistent with the public health, that evaluations are going forward in good faith, and that they will be completed as soon as reasonably practicable. The agency carefully explained in its Federal Register notices and response to the rulemaking petition that extra time was needed for review of completed tests and in some cases the conduct of additional tests; a special scientific review panel was involved in this, and on completion of its work the agency would have to review its report. *See* 50 Fed. Reg. 35,783-84, 35,786-89 (1985); 51 Fed. Reg. 31,323 (1986) (extension for Red No. 3 until Nov. 3, 1986); J.A. in No. 86-5150 at 387-421 (FDA Commissioner's response to Public Citizen's petition requesting ban). Announcing its most recent extension of Red No. 3, the agency explained that more time was needed "[b]ecause of the complexity of the scientific issues being considered." 51 Fed. Reg. at 39,856 (extension until Nov. 3, 1987). The most recent extensions for Red No. 33 and Red No. 36 announced that these reviews were essentially complete and the agency intended to list these dyes permanently, but that further time was necessary for the agency to prepare adequate explanations of its decisions. 52 Fed. Reg. 33,573 (1987) (extending provisional status until November 3, 1987); *see also id.* at 15,945 (extension for same dyes until July 6, 1987), *id.* at 6,323 (extension until May 4, 1987). Although *McIlwain* dealt specifically with delays caused by the need for further testing, its logic applies with equal force where further evaluation of completed tests is required. To the extent that Public Citizen's complaint rests on the length of time already

taken and anticipated for review of these dyes, it is foreclosed by *McIlwain*.[19] Public Citizen's allegations of bad faith were not properly raised below, and in any event amount to no more than speculation.

Public Citizen also argues that provisional listing is permissible only when permanent listing is a reasonable possibility—an outcome precluded under this opinion if the outcome from the animal studies is positive. But this has not yet happened and may never happen. Neither Red No. 33 nor Red No. 36 has been found to induce cancer in humans or animals.

The situation is slightly less clear with regard to Red No. 3. The Commissioner explained, in denying Public Citizen's petition, that further evaluation was necessary to determine whether a carcinogenic effect observed in animal testing was caused by a secondary mechanism. J.A. in No. 86-5150, at 407-10. There was, to be sure, evidence linking a statistically significant increase in tumors to the dye, but the chain of causation has yet to be established. There was a possibility, the Commission explained, that the dye might have effected the rats' thyroid glands, with that effect in turn causing the tumors. *Id.* If this were established, then a no-effect level in rats might be established. *Id.*; *see also* 50 Fed. Reg. at 35,786-87. Until the agency arrives at a final decision as to this question, the question of the Delaney Clause's application is not ripe. We therefore express no opinion as to the applicability of the provision in this secondary-effect

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[19] We also find Public Citizen's claim that action on Red No. 3 has been "unreasonably delayed" under 5 U.S.C. § 706(1) to be without merit. Unreasonable delay must be determined in the statutory context. *Public Citizen Health Research v. Commissioner, Food & Drug Administration*, 740 F.2d 21, 35 (D.C. Cir. 1984). As *McIlwain* suggested, the statutory scheme for grandfathering color additives allows the time necessary for careful testing and also for careful review of data.

situation, and decline to disturb the judgment of the District Court.

CONCLUSION

In sum, we hold that the agency's *de minimis* interpretation of the Delaney Clause of the Color Additive Amendments is contrary to law. The listing decisions for Orange No. 17 and Red No. 19 based on that interpretation must therefore be corrected. As for the colors still on the provisional list, we affirm the judgment of the court below in No. 85-5150, in view of *McIlwain* and the lack of a finding of carcinogenicity in the dyes at issue.

So ordered.

APPENDIX B

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 74, 81, and 82

[Docket No. 83C-0102]

Listing of D&C Orange No. 17 for Use in Externally Applied Drugs and Cosmetics

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is permanently listing D&C Orange No. 17 as a color additive for use in externally applied drugs and cosmetics. FDA is taking this action because it has concluded that the use of this color additive in externally applied drugs and cosmetics is safe within the meaning of section 706 of the Federal Food, Drug, and Cosmetics Act. This action responds to a petition filed by the Cosmetic, Toiletry and Fragrance Association, Inc.

DATES: Effective September 9, 1986, except as to any provisions that may be stayed by the filing of proper objections; objections by September 8, 1986. FDA will publish notice of the objections that the agency has received or lack thereof in the Federal Register.

ADDRESS: Written objections to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Gerad L. McCowin, Center for Food Safety and Applied Nutri-

tion (HFF-330), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-472-5676.

SUPPLEMENTARY INFORMATION:

I. Introduction

In 1960, Congress passed the Color Additive Amendments (the amendments). In *Certified Color Mfg. Ass'n* v. *Mathews*, 543 F.2d 284, 286-287 (D.C. Cir. 1976), the United States Court of Appeals for the District of Columbia Circuit explained the purpose of this legislation:

> The Color Additive Amendments of 1960 reflect a Congressional and administrative response to the need in contemporary society for a scientifically and administratively sound basis for determining the safety of artificial color additives, widely used for coloring food, drugs, and cosmetics. The Amendments reflect a general unwillingness to allow widespread use of such products in the absence of scientific information on the effect of these products on the human body. The previously used system had some glaring deficiencies, and the 1960 Amendments were designed to overcome them. * * *
>
> [Footnotes omitted.]

As amended, the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.) (the act) provides in section 706(a) (21 U.S.C. 376(a)) that a color additive will be deemed unsafe for use in food, drugs, cosmetics, and some medical devices unless FDA has issued a regulation permanently listing that color additive for its intended use. FDA will issue such a regulation only if it has been presented with data that establish with reasonable certainty that no harm will result from the use of the color additive. The burden of presenting such data is on the person who is seeking approval of the use of the additive.

In passing the amendments, Congress provided for the provisional listing of the color additives in use at that time, pending completion of the scientific investigations needed for a determination about the safety of these additives (section 203(b) of the transitional provisions of the amendments, Title II, Pub. L. 86-618, 74 Stat. 404-407 (21 U.S.C. 376, note)). Section 81.1 (21 CFR 81.1) of the agency's color additive regulations enumerates those color additives that are still provisionally listed. Among them is D&C Orange No. 17 for use in externally applied drugs and cosmetics. Because D&C Orange No. 17 was in use at the time the amendments were enacted, it had been provisionally listed for drug and cosmetic use in the Federal Register of October 12, 1960 (25 FR 9759).

II. Regulatory History

A. The Color Additive

D&C Orange No. 17 is principally 1-[(2,4-dinitrophenyl)azo]-2-naphthalenol (CAS Reg. No. 3468-63-1). Although it is identified in § 82.1267 (21 CFR 82.1267) as 1-(2,4-dinitrophenylazo)-2-naphthol, these two descriptions are synonymous.

B. Color Additive Petition

D&C Orange No. 17 is the subject of a color additive petition (CAP 9C0090) that was submitted on April 14, 1969, by the Toilet Goods Association, Inc. (now the Cosmetic, Toiletry and Fragrance Association, Inc. (CTFA), 1110 Vermont Ave. NW., Washington, DC 20005). FDA published a notice of filing of the petition in the Federal Register of August 6, 1973 (38 FR 21199). The petition, filed under the provisions of section 706 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 376), requested the permanent listing of D&C Orange No. 17 for coloring lipsticks, ingested drugs, and externally applied drugs and cosmetics.

In a letter dated May 14, 1974, the petitioner requested that the petition be amended to include listing D&C Orange No. 17 for eye-area use. FDA published an amended filing notice for the petition in the Federal Register of March 5, 1976 (41 FR 9584), to include the listing of D&C Orange No. 17 for eye-area use. FDA notified the petitioner by letters dated May 14, 1976, August 15, 1977, and August 4, 1978, of the need for data to support the use of D&C Orange No. 17 in cosmetics intended for use in the area of the eye. In a letter dated October 24, 1978, FDA advised the petitioner to consider withdrawing that portion of the petition that sought approval of the use of D&C Orange No. 17 in cosmetics intended for use in the area of the eye because it appeared that the required data from eye-area studies would not be readily available.

The petitioner did not submit the required data. Therefore, in a notice published in the Federal Register of April 1, 1983 (48 FR 14045), FDA announced that that portion of the petition relating to the listing of D&C Orange No. 17 for eye-area use was withdrawn without prejudice to a future filing. Eye-area use of D&C Orange No. 17 had never been provisionally listed.

In the Federal Register of February 4, 1977 (42 FR 6991), FDA published revised provisional regulations which required new chronic toxicity studies on 31 color additives, including D&C Orange No. 17, as a condition for continued provisional listing of these additives. FDA required the new chronic studies because the toxicity studies that the petitioners had submitted were deficient in several respects. FDA described these deficiencies in the Federal Register of September 23, 1976 (41 FR 41863):

1. Many of the studies were conducted using groups of animals i.e., control and those fed the color additive, that are too small to permit conclusions to be drawn on the chronic toxicity or carcinogenic potential of the color. The small number of animals used

does not, in and of itself, cause this result, but when considered together with the other deficiencies in this listing, does do so. By and large, the studies used 25 animals in each group; today FDA recommends using at least 50 animals per group.

2. In a number of the studies, the number of animals surviving to a meaningful age was inadequate to permit conclusions to be drawn today on the chronic toxicity or carcinogenic potential of the color additives tested.

3. In a number of the studies, an insufficient number of animals was reviewed histologically.

4. In a number of the studies, an insufficient number of tissues was examined in those animals selected for pathology.

5. In a number of the studies, lesions or tumors detected under gross examination were not examined microscopically.

In the February 4, 1977, order, FDA postponed the closing date for the provisional listing of D&C Orange No. 17 until January 31, 1981, for the completion of the new chronic toxicity studies. In the Federal Register of March 27, 1981 (46 FR 18958), the agency established a new closing date of March 31, 1983, for the completion of the chronic toxicity studies and the submission of data to FDA on a prescribed schedule.

In the Federal Register of April 1, 1983 (48 FR 13976), FDA announced that the provisional listing of the use of D&C Orange No. 17 for coloring ingested drugs and cosmetics had expired (48 FR 13976) and denied that portion of the petition that requested the listing of D&C Orange No. 17 for ingested drug and cosmetic uses (48 FR 14045). FDA took the latter action because it concluded, on the basis of the animal experiments that had been performed as a condition of the provisional list-

ing of D&C Orange No. 17, that the color additive was carcinogenic when administered in the diet of laboratory animals. As a result of these actions, D&C Orange No. 17 could not be added to ingested drugs and cosmetics after April 1, 1983. D&C Orange No. 17 remained provisionally listed for use in externally applied drugs and cosmetics.

As discussed in the Federal Register of April 1, 1983 (48 FR 14047), the petitioner continued to seek permanent listing for the use of this color additive in external cosmetic and drug products that are not subject to incidental ingestion. On March 22, 1983, CTFA submitted preliminary results of a percutaneous absorption study of D&C Orange No. 17. Another CTFA submission, dated April 15, 1983, included a review and analysis of scientific studies, including an assessment of the risk from the use of D&C Orange No. 17 in external cosmetic and drug products, a final report on percutaneous absorption of D&C Orange No. 17, and a discussion of the legal issues raised by external use of this color additive. The agency agreed to review these submissions before reaching a conclusion on the safety of the use of D&C Orange No. 17 in externally applied drugs and cosmetics. Because its review of the CTFA submissions and of the scientific and legal issues raised by this matter took longer than the agency anticipated, FDA had to extend the provisional listing of this color additive on a number of occasions. The agency established the current closing date of August 6, 1986, for the provisional listing of D&C Orange No. 17 for use in externally applied drugs and cosmetics by a rule published in the Federal Register of June 6, 1986 (51 FR 20786). In that notice, the agency also announced its decision to permanently list the color additive for its external drug and cosmetic uses. The discussion that follows sets forth the basis for that decision and the agency's conclusion that the use of D&C Orange No. 17 as a color additive in externally applied

drugs and cosmetics is safe within the meaning of section 706 of the act.

C. Citizen Petition Filed by Public Citizen Health Research Group

On December 17, 1984, the Public Citizen Health Research Group (Public Citizen) petitioned FDA to ban the use of the color additives that remained provisionally listed. On January 22, 1985, Public Citizen filed a complaint in the District Court for the District of Columbia seeking the same relief. Public Citizen alleged that, by continuing to provisionally list the color additives, including D&C Orange No. 17, FDA had violated the Color Additive Amendments to the act, as well as those provisions of the Administrative Procedure Act (5 U.S.C. 706(1)) that pertain to unreasonable delay of agency action. Public Citizen sought to enjoin FDA from using the provisional list or any other means to allow the marketing of the provisionally listed color additives.

On June 21, 1985, the Commissioner of Food and Drugs sent to Public Citizen a detailed response to the petition. In his response the Commissioner carefully reviewed and discussed the arguments and information submitted in support of the petition. The Commissioner concluded that the public health would not be endangered by the continued marketing of the color additives while scientific, legal, and policy issues were addressed and, therefore, the Commissioner denied the petition.

On February 13, 1986, Judge Stanley S. Harris granted FDA's motion for summary judgment and dismissed Public Citizen's complaint. *Public Citizen et al.* v. *DHHS, et al.*, No. 85-1573 (D.D.C. February 13, 1986). Public Citizen has appealed Judge Harris' decision.

III. Review of Provisionally Listed Color Additives by a Scientific Review Panel

In the proposal to extend the closing dates for the provisional listing of certain color additives, including D&C Orange No. 17 (50 FR 26377, June 26, 1985), FDA announced that the Commissioner had established a scientific review panel (panel) of Public Health Service scientists to evaluate data and report on the risk assessment issues presented by the use of six color additives: D&C Red No. 8, D&C Red No. 9, D&C Red No. 19, D&C Red No. 37, D&C Orange No. 17, and FD&C Red No. 3.

FDA asked the panel to consider several scientific issues that had been raised by FDA scientists about whether a reliable assessment of the risk from the use of these additives could be conducted. Specifically, one issue was whether, for each additive, unidentified contaminants, rather than the principal color component, could be responsible for the observed carcinogenic effects in animal testing, and whether any such unknown impurities or components may be absorbed through the skin to a greater or lesser extent than other parts of the additive. The panel was charged with examining this impurities issue and further with addressing the issue of whether a risk assessment calculation could be made from the available data, and, if so, whether the risk assessments before the agency were properly calculated.

In the Federal Register of March 6, 1986 (51 FR 7856), FDA announced the availability of the final report of the panel. The report is entitled "Report of the Color Additive Scientific Review Panel, September 1985, Docket No. 86N-0039." A copy of the report is available to the public for review at the Dockets Management Branch (address above). Requests for copies of the report should be identified with Docket No. 86N-0039.

In the report, the panel concluded that the risk assessments submitted by the petitioner for several of the color

additives, including D&C Orange No. 17, are consistent with current acceptable usages in risk assessment. The panel also concluded that legitimate issues with regard to impurities had been raised but could be addressed by making reasonable and appropriate assumptions about the possible influence that such impurities might have. The panel concluded that the range of lifetime risk presented by external exposure to D&C Orange No. 17 was extremely low. The report of the panel was also submitted to peer review and subsequently published in *Risk Analysis*, 6:2:117-154, 1986, hereby broadly providing the risk analysis assessment to the scientific community. These findings will be discussed in greater detail below.

IV. Overview of the Final Rule

FDA has evaluated all the available evidence regarding the safety of D&C Orange No. 17. Based upon this evaluation, FDA finds that the use of D&C Orange No. 17 in externally applied drugs and cosmetics is safe. Although the external uses involve, based on conservative statistical analysis, a theoretical carcinogenic risk, the agency finds that this risk is so trivial as to be effectively no risk at all. For these reasons, the agency has decided to permanently list these uses of D&C Orange No. 17.

The remainder of this document describes the information and advice relied upon by the agency in reaching its conclusion as to the safety of D&C Orange No. 17 as a color additive for externally applied drugs and cosmetics. First, the agency evaluates the available data resulting from toxicology testing of D&C Orange No. 17 and then discusses CTFA's safety evaluation of these data. Next the agency deals with CTFA's arguments and questions concerning the relevance of the toxicology tests to the determination of the safety of the external drug and cosmetic uses of D&C Orange No. 17. In the following section, FDA discusses CTFA's assessment of the extent of

human exposure resulting from the external drug and cosmetic uses of D&C Orange No. 17.

In the remaining sections, FDA discusses CTFA's low dose carcinogenic risk assessment approach, the report of the panel, and the panel's conclusions regarding the propriety of relying upon the available data to conduct risk assessments for use by a government regulatory agency. The final section discusses the agency's reliance on the *de minimis* doctrine to reach the conclusion that the proscriptions of the Delaney Clause should not be invoked in this matter.

V. Toxicology Testing of D&C Orange No. 17

A. *Discussion: Summary of Studies Submitted by CTFA*

To establish that D&C Orange No. 17 is safe for use in drugs and cosmetics, CTFA submitted reports on a number of animal toxicity studies for the color additive. Among these studies were chronic and subchronic feeding studies in dogs and rats, a three-generation reproduction study in rats, teratology studies in rats and rabbits, a dermal study in rabbits, and an 18-month skin painting study in mice. These studies did not produce any evidence that the use of this color additive, for the petitioned uses, would be unsafe.

The 18-month skin painting study, which is relevant to the use of D&C Orange No. 17 in externally applied drugs and cosmetics, was performed using 2 groups, each consisting of 50 male and 50 female Swiss-Webster mice. One group, the controls, was treated with distilled water, while the test group was treated with D&C Orange No. 17 applied as a 1 percent aqueous suspension, in terms of the pure color. Treatment consisted of the application of 0.1 milliliter of the test material to the clipped backs of each animal two times per week. Observations were made daily for mortality and twice weekly for gross toxicity.

Animals that died, those sacrificed as being moribund, and those surviving the 18-month study were autopsied. Tissues sectioned and examined microscopically included skin and grossly abnormal organs and tissues from 27 female control animals, 25 male control animals, and all animals in the experimental group. Complete pathology was performed on five males and five females from the control animals and five males and five females from the tested group.

Results from the treated and untreated animals were essentially similar, as were survival patterns. Tissue masses were observed in the areas of repeated dermal application of the color in two mice. One was a wartlike growth that could not be located in the fixed tissue and the other was identified as a papilloma. Two control animals were also found to have lesions in or beneath the skin. The lesions were identified as a subcutaneous, undifferentiated sarcoma and the second as a subcutaneous anaplastic osteogenic sarcoma. Dermal effects such as acanthosis, hyperkeratosis, and dermatitis were somewhat increased in the experimental group when compared to the controls.

Although no evidence of compound-related neoplastic responses was found in these skin painting or chronic feeding studies, FDA concluded that the sensitivity of the chronic feeding studies was insufficient under current standards to provide the requisite demonstration of safety for ingested use. Therefore, in the February 4, 1977, order, FDA required additional chronic feeding studies on D&C Orange No. 17. The studies were conducted for the petitioner at Bio/dynamics, Inc., East Millstone, NJ. These studies included a long-term feeding study in mice and a chronic toxicity/carcinogenicity study, with in utero exposure to D&C Orange No. 17, in rats. The final reports for these studies (CAMF #9, Entries 510, 511, 512) were received by the agency on March 31, 1982.

The new long-term chronic studies represent current state-of-the-art toxicological testing. The protocols for these studies have benefited from knowledge of deficiencies in previously conducted carcinogenesis bioassays and other chronic toxicity protocols. The use of large numbers of animals of both sexes, pilot studies to determine maximum tolerated dosages, two control groups (thereby effectively doubling the number of controls), and in utero exposure in one of two species tested significantly increases the power of these tests to detect dose-related effects. The studies were designed and conducted in compliance with FDA's good laboratory practice regulations (21 CFR Part 58) and were subject to inspections by FDA officials during their course.

B. Evaluation of the Long-Term Studies

1. Long-term Feeding Study in Rats

The long-term feeding study in rats included in utero exposure to D&C Orange No. 17. Charles River Albino (CD) rats (parental animals) were randomly assigned (60 males and 60 females per group) and mated to produce the F_1 generation. D&C Orange No. 17 was mixed with standard laboratory chow and fed ad libitum to the parental animals during their mating and gestation period and to their offspring (the F_1 generation animals) during the long-term feeding study. Two separate groups of rats served as controls.

The petitioner, in meeting with FDA on September 12, 1977, discussed the adequacy of the protocol for this chronic feeding study. FDA's scientists indicated that the proposed dosage levels (i.e., 0.00, 0.02, 0.05, and 0.10 percent) were too low. On the basis of data from earlier studies on D&C Orange No. 17, FDA's scientists concluded that survival and weight data suggested that lifetime studies could be successfully carried out in rats using 1.0 percent as the maximum dosage level. The

agency, therefore, asked the petitioner to conduct an additional rat chronic feeding study with a 1.0 percent dosage level of D&C Orange No. 17 (Ref. 10). This study was carried out with the same strain of rats and with the same experimental design as the original study. It included a treatment group and a concurrent control group.

Seventy F_1 rats of each sex, obtained from the reproduction phase of the study, were randomly selected and distributed into dosage groups similar to those described above for their parental animals and were used for the chronic feeding phase of the study (26 months for males and 30 months for females). Survival and body weights of female rats from the chronic feeding phase were unaffected by treatment. However, treated male rats in this phase exhibited decreased survival as well as decreased body weights at the highest dose (1.0 percent diet) (Ref. 1). Except for discoloration of the urine, there were no hematological or clinical findings that could be ascribed to treatment. Increased deposition of pigment in the spleen of female rats was noted in the 1.0 percent group.

Among female rats, at the 1.0 percent dietary level of D&C Orange No. 17, there was a marked and statistically significant increase in animals with hepatocellular tumors (neoplastic nodules and carcinomas combined) compared to the concurrent control group animals (21/70 in the 1.0 percent dose group versus 3/70 in the concurrent control group, $p=0.0001$, prevalence analysis; 70 is the number of animals entered into the study). The denominators reflect the number of livers for which tissue was available for microscopic examination, including the 10 animals in each group which were interim sacrificed after approximately 1 year of treatment according to protocol. They represent the number of livers examined by FDA pathologists. The prevalence statistical analysis, however, is a time-adjusted test. It takes into account deaths, including interim sacrifice deaths, that are incidental to the

finding of liver neoplasms. The incidence of animals with non-neoplastic liver lesions (foci of cellular alteration) was also increased among female rats in the 1.0 percent dose group when compared to the control group.

Additionally, multiple hepatocellular tumors (neoplastic nodules) were noted only in the 1.0 percent D&C Orange No. 17 treated group females. Moreover, the number of animals with multiple occurrences of foci of cellular alteration (non-neoplastic lesion) and of animals that had multiple classifications, i.e., foci of cellular alteration and neoplastic nodules, present in the same microscopic section of liver was higher among treated group females (1.0 percent dose group) than in the concurrent control group. The 1.0 percent dose group females had increased liver weights as well. The liver data in the 1.0 percent study indicate a clear-cut treatment-related effect in the occurrence of hepatocellular tumors in female rats as a result of the administration of D&C Orange No. 17. Liver weights relative to body weights were also increased in both male and female rats that received 0.10 percent D&C Orange No. 17 in the diet, indicating further that the liver is the target organ for D&C Orange No. 17 toxicity.

The petitioner provided historical control data for hepatocellular tumors in Charles River Albino female rats from 12 separate control groups from studies conducted at Bio/dynamics, Inc. The average incidence of hepatocellular tumors (neoplastic nodules and carcinomas combined) was 9.4 percent. In contrast, the incidence of hepatocellular tumors in the high-dosage (1.0 percent) group was 30 percent, far exceeding the average spontaneous incidence.

Thus, the long-term feeding exposure of Charles River CD Albino rats to a 1.0 percent dose level of D&C Orange No. 17 produced the carcinogenic effect of a statistically significant increase in the number of female rats with hepatocellular neoplasms compared to the control groups.

2.. Long-Term Feeding Study in Mice

Charles River CD-1 mice of both sexes were randomly assigned to one of three treatment groups receiving D&C Orange No. 17 in the diet at concentrations of 0.025, 0.25, and 1.0 percent or to one of two control groups and fed the test diets for approximately 23 months for the males and 25 months for the females. The selection of these dosage levels was based on the results of a 90-day range-finding study.

The incidence of hepatocellular neoplasms (adenomas and carcinomas) among male mice was increased in a dose-related manner ($p=0.00004$, trend test). The incidence of hepatocellular neoplasms in male mice was 8/58 and 8/59 or 16/117 for the two control groups, and 11/58, 13/57, and 19/56 for the low-, medium-, and high-dose groups, respectively. Again, as with the rats, the denominators reflect the number of livers for which tissue was available or was adequate for microscopic examination by FDA pathologists. A few missing and autolyzed tissues account for the less than 60 per group expected from the initial number of animals started on test. The appropriate time-adjusted prevalence analysis was performed on the incidences. A small increase, compared to the corresponding control group animals, in the number of female mice with hepatocellular neoplasms in the mid- and high-dose groups was also reported. Thus, the long-term feeding exposure of Charles River CD-1 mice of D&C Orange No. 17 was associated with a significant dose-related increase in the number of male mice with hepatocellular neoplasms compared to the control groups.

Survival of male mice fed the D&C Orange No. 17 diets was decreased in a dose-related manner ($p=0.0005$, Cox's time-adjusted trend test), but survival of female treated mice apparently was not adversely affected by treatment. Similarly, body weights of high-dose male mice were slightly less than controls, but no effect on body weights of treated female mice was seen.

Also, there was an increase in mortality noted in mid-dose and high-dose males as well as in mid-dose females. Aside from test material coloration of the coats of the treated animals, there were no significant treatment-related effects on general physical condition, body weights, food consumption, or incidence of palpable tissue masses. Mean hemoglobin concentration, hematocrit, and erythrocyte counts were often slightly reduced with concomitant increases in reticulocyte counts relative to control in the high-dose animals.

Microscopic examination revealed pigment deposition in the brain, spinal cord, thyroid, heart, and stomach in all treatment groups as well as in the spleen, cecum, and liver in the males and females in the high-dose group. The neurons of the brain and spinal cord of high-dose males and females were noted to have an increased incidence of neuronal basophilia. This was associated with the intracytoplasmic accumulation of pigment in animals at the high-dose level. High-dose female mice were observed to have an increased incidence of chronic myocarditis.

3. *Related information.* In addition to the results from the long-term feeding studies, D&C Orange No. 17 has been reported to be mutagenic to all standard tester strains of *Salmonella typhimurium* but not in the one mammalian system tested. One of its probable metabolites, 2,4-dinitroaniline, is also mutagenic to all tester strains, and another probable metabolite, 1-amino-2-naphthol, belongs to a chemical class that includes known carcinogens.

C. FDA's Conclusion Regarding the Ingested Uses of D&C Orange No. 17

No significant data base has been developed concerning the toxicity of D&C Orange No. 17 since the agency concluded in the Federal Register of April 1, 1983 (48 FR

14047), that the color additive was a carcinogen when administered in the diet of laboratory animals.

Based on these findings, the agency denied that part of CTFA's petition requesting permanent listing of D&C Orange No. 17 for use in ingested drugs and cosmetics (48 FR 14047; April 1, 1983). The agency also administratively withdrew that part of the petition requesting eye-area use because CTFA had failed to provide data in support of such a use.

VI. CTFA's Safety Arguments

In its submissions, CTFA presented several arguments that raise questions about the relevance of the ingestion studies to a determination of the safety of the use of D&C Orange No. 17 to color externally applied drugs and cosmetics. In the following sections, the agency reproduces the arguments and its internal evaluation of them.

A. Interpretation of Maximum Tolerated Dose

In the submission dated April 15, 1983, CTFA asserted that the 1.0 percent dose level of the second rat study substantially exceeded the maximum tolerated dose and thus violated the National Cancer Institute (NCI) guidelines for carcinogenicity testing.

The NCI guidelines define the maximum tolerated dose as "the highest dose of a test agent given during the chronic study that can be predicted not to alter the animals' normal longevity from effects other than carcinogenicity" (Ref. 1). The guidelines also state that the maximum tolerated dose "should be the highest dose that causes no more than a 1.0 percent weight decrement, as compared to the appropriate control groups; and does not produce mortality, clinical signs of toxicity, or pathogenic lesions (other than those that may be related to a neoplastic response) that would be predicted to shorten the animals' natural life span" (Ref. 1). The purpose of

establishing the maximum tolerated dose is to assure that the test animals are challenged but not killed by the non-carcinogenic toxic effects of high doses of a substance. Early death would obscure any carcinogenic effects of the substance being tested.

The question whether the maximum tolerated dose was exceeded is relevant only to the female rats, among whom the increase in liver neoplasms was found. The feeding of D&C Orange No. 17 at the highest dietary level to these animals had no effect on their survival when compared to the controls. Application of the NCI computer program for tumor mortality analysis to the female survival data yields a Cox statistic (time-adjusted, continuity corrected) with a probability of 0.32 and a Breslow statistic (time-adjusted) with a probability of 0.19. These numbers indicate that the females' survival was not affected by the feeding of D&C Orange No. 17. Further, no difference in the average body weights was observed between treated and control female rats. In addition, there were no clinical signs of toxicity or post-mortem lesions other than those related to the neoplastic response. Therefore, the agency concludes that, for the female rats, the maximum tolerated dose was not exceeded and that CTFA's contention that the study violated NCI guidelines for carcinogenicity testing is not substantiated.

B. Significance of Mouse Liver Tumors

In its April 15, 1983 submission, CTFA questioned the significance of the mouse liver tumors observed in the chronic tests. First, CTFA contended that reliance on the male mouse liver tumors is controversial because many strains of mice have a high incidence of liver tumors and retrovirus infection. Second, CTFA argued that the observed male mouse liver tumors were associated only with severe liver toxicity at the feeding level of 1 percent of the color additive in the diet and that this level exceeded

the maximum tolerated dose. Finally, CTFA stated that, in any event, the male mouse liver tumors were statistically significant compared only to the controls in this study but not to the controls in other recent studies, thus suggesting that the tumors were not, in fact, an event worthy of attention.

Some members of the scientific community have argued that a compound should not be regarded as carcinogenic if the only evidence of carcinogenicity is an increase in hepatomas in the mouse liver because many inbred mouse strains have a high background incidence of these neoplasms. According to this argument, the tumors indicate the presence of a latent population of initiated tumor cells rather than a carcinogenic effect of the compound.

The liver, because of its location and important role in metabolism, is a frequent target organ for toxic effects of compounds administered by the oral route. Substances absorbed from the gastrointestinal tract reach the liver in amounts much higher than the amounts to which other organs are generally exposed. Metabolic conversion of a substance to a more toxic metabolite often occurs in the liver, and the liver cells are exposed to the highest concentration of the active agent. Thus, hepatotoxic effects may be the only toxic effects observed. For this reason, the agency believes that the liver tumors must be carefully considered. FDA's Cancer Assessment Committee reviewed the data and CTFA's arguments and reached the following conclusions:

CTFA's argument about the high background incidence of liver cancer in mice does not apply to the CD-1 mouse, the strain used in the mouse study. The background incidence of hepatocelluiar tumors in this strain is low compared to most mouse strains. Moreover, data submitted by CTFA on April 8, 1981, showed the following incidence of tumors in 16 control groups (more than 900 mice of each sex):

	Males	Females
Hepatocellular carcinoma	9.65% ± 4.25%	0.63% ± 1.03%
Hepatocellular adenoma	5.12% ± 3.92%	1.17% ± 1.21%

Thus, the incidence of hepatocellular tumors (carcinomas and adenomas) among male mice in the control groups was about 15 percent. In contrast, the incidence of hepatocellular tumors among male mice in the high-dose group was about 34 percent.

Moreover, CTFA's argument concerning exceeding the maximum tolerated dose is misplaced. The argument is only relevant to the high-dose male mouse group in which the increase in hepatocellular neoplasms was observed. Although body weights and survival of mice in this group were slightly affected, no significant treatment-related effects were observed aside from material coloration of the coats of the animals. As discussed above, the purpose of establishing the maximum tolerated dose is to assure that the test animals are appropriately challenged but are not killed by the noncarcinogenic toxic effects of high doses of the substance. In the absence of any observed significant treatment-related effects other than the hepatocellular neoplasms, the committee concluded that the maximum tolerated dose was not exceeded in the study.

Finally, CTFA's argument concerning the limited statistical significance associated with the male mouse liver tumors was evaluated. In this study with D&C Orange No. 17, the incidence of male mice with hepatocellular tumors was increased in comparison to the concurrent controls at both the mid- and high-dose levels, and the increase was dose related (Trend Test $p=0.00004$). Furthermore, the historical control and concurrent control values are very similar. Consequently, the tumor incidence in treated mice is greater than the historical control values. There is also a dose-related increase in the

numbers of male mice with malignant tumors (i.e., hepatocellular carcinomas) (Trend Test p=0.046).

The International Expert Advisory Committee to the Nutrition Foundation (Ref. 2) described the following factors as important in determining whether the production of mouse hepatocellular tumors is the result of treatment: (1) Incidence of tumors in treated animals is clearly higher than in concurrent controls; (2) Incidence is also higher than in historical controls or dose related; (3) There is a decrease in time of onset in the treated animals; (4) There is a preponderance of malignant lesions in treated animals compared with the controls; and (5) Tumors are observed at other sites in the mouse, or tumors are observed in other species. Each of these conditions was reviewed in the case of D&C Orange No. 17, and, accordingly, the committee concluded that the hepatocellular tumors observed in the male mice were the result of the ingestion of D&C Orange No. 17. (The panel also reviewed available data on the rat and mouse bioassays of D&C Orange No. 17. Although the panel reached different conclusions with respect to the mouse bioassay, this difference is inconsequential, in light of the fact that the rat has been shown to be the most sensitive test species and the 1.0 percent feeding study in rats provides the best data base from which to estimate the likely risks to man presented by exposure to the external uses of D&C Orange No. 17.)

C. Mechanism of Carcinogenicity and Significance of "Benign" Tumors

In its April 15, 1983, submission CTFA offered the following arguments concerning the significance of benign tumors: "[In the female rat], only the incidence of benign hepatocellular adenomas (neoplastic nodules) was increased. There was no significant increase in the incidence of malignant carcinomas in the treated female. Nor was there any effect in the males fed the same level of color additive. This indicates a very weak effect apparently occurring only at high doses that are toxic to

the liver. This suggests an indirect mechanism of neoplasia secondary to toxic damage." (Petitioner's Submission of April 15, 1983, p. 21.)

FDA agrees that the increase in the incidence of malignant hepatocellular carcinomas in the 1.0 percent dose group of the female rat would not be statistically significant if malignant hepatocellular carcinomas alone were considered. However, FDA notes that on the issue of "benign" and "malignant" tumors, a 1979 report of the Interagency Regulatory Liaison Group stated: "Carcinogenic and chronic toxic effects of a chemical on an organ, tissue or cell develop through a series of stages from minimal changes to advanced and possibly fatal end points. The stage reached at any particular time is related to the dose of a substance, the conditions of exposure, the time elapsed since the beginning of exposure and host susceptibility factors. Early lesions that are pathognomonic of a disease process resulting from toxic chemicals should be grouped with more advanced lesions, whether or not the animal has survived long enough for the process to develop to the latest stage." (Ref. 3.)

FDA agrees with this analysis and believes that it is appropriate to combine hepatocellular neoplasms (neoplastic nodules, adenomas, and carcinomas) for analysis because all of these lesions could be concurrent or sequential stages in the neoplastic process (Ref. 4).

In the case of D&C Orange No. 17, the incidence of female rats with benign and malignant hepatocellular tumors (neoplastic nodules and hepatocellular carcinomas, respectively) was analyzed both separately and combined. When a Fisher's Exact Test was applied to compare the incidence of animals with a neoplastic nodule in the 1 percent D&C Orange No. 17 dose group with that of the control group, a *p*-value of less than 0.01 was found. The agency also did a prevalence analysis, which yielded a Cox statistic corresponding to a probability of less than 0.001, thereby reinforcing the results of the Fisher's Ex-

act Test. The p-value calculated from the combined incidence of animals with a neoplastic nodule or a hepatocellular carcinoma was even smaller. This information leads the agency to conclude that D&C Orange No. 17 most likely exhibits a primary effect. CTFA has offered no evidence to the contrary.

CTFA also suggested in its submission that the female rat liver tumors in the 1 percent dose group are caused by an "indirect mechanism of neoplasia secondary to toxic damage * * *." However, CTFA has not submitted any scientific evidence to support such a hypothesis.

D. Percutaneous Absorption Studies With D&C Orange No. 17

On April 15, 1983, CTFA submitted its final report of an in vitro percutaneous absorption study on D&C Orange No. 17. An in vitro percutaneous absorption test is designed to measure the ability of a substance, such as a color additive, to penetrate excised skin under conditions simulating human use. Information on skin penetration is important for determining the systemic exposure to a color additive used in topical applications.

The study was performed, in general, in a satisfactory manner. The test data clearly show that radiolabeled material from D&C Orange No. 17 passes through the skin in small but measurable amounts. Therefore, the agency concluded that some systemic exposure to a portion of the color additive may occur from the use of externally applied drugs and cosmetics containing D&C Orange No. 17.

The assessment of the carcinogenic risk from the use of an externally applied carcinogenic color additive is determined by (1) the amount of color additive applied to the skin and the frequency of application, (2) the concentration of carcinogenic agents in the color additive, (3) the potency of the carcinogenic agents, and (4) the fraction of the applied carcinogenic agents that penetrates the skin.

The risk estimates submitted by CTFA are based on the assumptions (1) that the principal color component is the carcinogenic agent, (2) that the radiolabeled material penetrating skin is representative of the whole color additive, and (3) that 100 percent of the carcinogenic agent is absorbed from the alimentary tract into the blood stream in the animal feeding studies.

FDA's scientists questioned CTFA's assumptions because an argument could be made that a contaminant is responsible for the carcinogenic response. Color additives are not pure substances and normally contain intermediates, subsidiary colors, and other contaminants from intermediates and from side reactions. Although the carcinogenicity of D&C Orange No. 17 was revealed by an animal bioassay, the bioassay did not establish whether the carcinogenic response was produced by the principal color component or by one or more of its contaminants. It is theoretically possible that one of the contaminants could be responsible for the production of the carcinogenic response.

CTFA's assumption that the radiolabeled material was representative of the whole color additive (and, that, therefore, there is no need to be concerned with possible impurities) could not be substantiated. CTFA measured only the radioactivity of the substance that penetrated the skin and could not identify the components that actually penetrated the skin.

In addition, FDA scientists could not determine from the data submitted by CTFA which constituents of the color additive penetrated skin, or whether impurities in the color additive would penetrate skin in the same manner as the primary color that was tested. It is possible (1) that the actual carcinogen could be a contaminant that penetrated the skin but was unlabeled and therefore undetected; (2) that virtually none of the principal color component penetrated the skin, and that the radioactive material found could be due to carcinogenic contami-

nants; and (3) that the degree of skin penetration by the actual carcinogenic agent is greater than that estimated by CTFA based on its assumption that the principal color component of D&C Orange No. 17 is the carcinogen.

CTFA's assumption that 100 percent of the carcinogenic agent is absorbed from the gastrointestinal tract was questioned by FDA's scientists because few chemicals are ever completely absorbed. There are many reasons for poor or limited absorption of chemical substances from the gastrointestinal tract, including (1) the instability of the chemical in acidic fluids, (2) enzymatic breakdown by digestive juices, (3) destruction by intestinal microorganisms, and (4) lack of lipid solubility.

FDA asked the panel to review CTFA's assumptions and the agency's concerns about impurities. The panel revised several of CTFA's assumptions and concluded that the agency's concerns regarding impurities, although important, could be addressed by making reasonable and appropriate assumptions about the possible effects impurities might have. The panel found it highly unlikely that impurities would significantly influence the risk assessment. The results of the panel's review are discussed in greater detail in a later section of this notice.

VII. CTFA's Assessment of Exposure to D&C Orange No. 17

In the report submitted to FDA on April 15, 1983, CTFA outlined the approach used in the CTFA risk assessments to estimate human exposure to D&C Orange No. 17. The cumulative amount of D&C Orange No. 17 absorbed by an individual was determined, based upon the products in which the color additive was used, the amount of each product used per application, the frequency of use of each product, the concentration of the color additive in each product, and the level of dermal absorption.

CTFA reported that by using both a prospective and a retrospective approach, it had determined the exposure to D&C Orange No. 17 through external cosmetic and drug product use. Data on the frequency of use of various external cosmetic and drug products came from two sources. The first is a 1-week prospective survey of female participants. The participants recorded the number of times in a week they used a range of cosmetic products including face powders and rouges, hair cosmetics, nail products, bathwater products, wash-off products, and various other externally applied cosmetic products. For products used less often than once per week, they were asked to report how often they generally used such products. The second source of data on frequency of use is from a retrospective survey of 1,129 customers of a chain of stores run by a major cosmetic manufacturer. Because the individuals in this survey were customers of specialty cosmetic stores, they are likely to have above-average usage patterns. For both sets of data, for each product, CTFA listed an average and an upper 90th percentile value of frequency of usage.

Data on the amount of each product per application were provided from the responses to a survey of CTFA member companies to obtain the results of existing studies on this subject. The values are the averages for each product as reported in CTFA's survey.

The April 15, 1983, report presented data derived from the skin absorption study conducted by Dr. Thomas J. Franz on the proportion of the D&C Orange No. 17 contained in each product that is likely to be absorbed. The skin absorption study conducted by Dr. Franz is described in detail in a separate report (Ref. 9). Briefly, the absorption of ^{14}C-labelled D&C Orange No. 17 through half-thickness human abdominal skin was studied using Franz diffusion cells. Absorption under each of four experimental conditions described in the study was tested on duplicate sections of skin from each of three donors.

The receptor phase (isotonic saline, pH 7.6, 37° C) was sampled for radioactivity and replaced by fresh saline at 4, 8, and 12 hours, and at 12-hour intervals until four steady-state readings were obtained, or 72 hours after application of the color additive. The daily absorption rates and the percentage of the applied color additive absorbed over 3 days were calculated.

CTFA believes that the amount of D&C Orange No. 17 applied per square centimeter in these experiments was similar to or greater than the corresponding amount that would be applied in externally applied cosmetics and drugs. Hence, it concluded that the experimental permeability data are likely to be reasonably applicable to absorption of the color additive from a cosmetic or drug applied to the skin.

CTFA provided estimates of the amount of the color additive absorbed daily by combining the information on daily usage (upper 90th percentile) of the external cosmetic and drug products with data on the D&C Orange No. 17 content of the products (average and maximum) and estimates of the proportion of the color additive absorbed. CTFA emphasized that these data were deliberately chosen to overestimate exposure.

The usage values are upper 90th percentile values. The concentration of D&C Orange No. 17 is presented both as the maximum used in any formulation of each product type and as the average concentration in formulations that contain D&C Orange No. 17. For all product categories, there are many formulations that do not contain D&C Orange No. 17. Thus, a true "average" would be much lower, and the "average" values listed greatly overestimate the extent of exposure to D&C Orange No. 17 from its use in externally applied cosmetic and drug products.

By summing the values of D&C Orange No. 17 absorbed per day for each product containing the color addi-

tive, CTFA determined the "worst case" maximum amount absorbed for all or any combination of products. Summing all values gives a daily "worst case" absorption of 0.015 to 0.021 microgram or 0.00029 to 0.00039 microgram per kilogram per day for a 53 kilogram adult female using all products containing the maximum level of D&C Orange No. 17 at the upper 90th percentile usage frequency.

The panel, at FDA's request, critically evaluated CTFA's assessments and the underlying assumptions. A discussion of the panel's evaluation is provided in a later section of this notice.

VIII. CTFA's Low-Dose Carcinogenic Risk Assessment Approach

CTFA calculated both the "best conservative estimate" and the "upper bound estimates" of risk from the use of D&C Orange No. 17 in externally applied cosmetics and drugs, using currently accepted methods of risk assessment. The low-dose risk assessment proceeds in four steps:

1. Selection of the set of data on tumor incidence judged most appropriate as the basis for inference of human risk;

2. Extrapolation of these data to provide "best estimate" calculations, thus providing a range of risk to mice and rats at low-dose levels;

3. Extrapolation of the potential risk to humans at low-dose levels; and

4. Calculation of the potential risk of humans at the likely level of exposure from known patterns of use.

CTFA acknowledged that each of these steps required the use of assumptions with varying degrees of certainty. It was standard procedure by CTFA to make highly conservative "worst case" assumptions at each step, so that

the final estimates likely overstated the actual risks by large factors. In its report, CTFA presented both "best conservative estimate" and "upper bound estimate" calculations to illustrate the range of potential risk. The "best conservative estimate" was based upon the extrapolation curve that best fits the experimental data, but also included such highly conservative "worst case" elements as the assumption that an individual consumer will be in the upper 90th percentile for frequency of use of all cosmetic products and will use only those cosmetic products that contain D&C Orange No. 17 at the maximum concentration. The "upper bound estimate" includes all "worst case" assumptions.

The CTFA risk assessment combined adenomas and carcinomas from the mouse liver tumor data and used the "worst case" maximum projections of human exposure and skin penetration. The multistage extrapolation model using the "worst case" maximum human exposure provides a "best conservative estimate" of potential lifetime risk to humans of $4x10^{-11}$ (1 in 25 billion), and an "upper bound estimate" of $7x10^{-11}$ (1 in 14 billion).

For the rat liver tumors, CTFA again combined both adenomas and carcinomas in order to provide a very conservative "worst case" estimate of potential risk to humans. The multistage extrapolation model using the "worst case" maximum human exposure provided a "best conservative estimate" of potential lifetime risk to humans of $1.1x10^{-19}$ (1 in 10 sextillion), and an "upper bound estimate" of $2.1x10^{-10}$ (1 in 4.8 billion).

IX. Review of D&C Orange No. 17 by the Scientific Review Panel

FDA's evaluation of the petitions for permanent listing of these color additives, and other available information, raised questions concerning whether CTFA's risk assessment was valid. As discussed above, FDA convened the panel to address these questions. The membership of

the panel is outlined in the Federal Register of June 26, 1985 (50 FR 26379), which is incorporated by reference.

The panel was charged to evaluate the available data, information, and views on the color additives and to provide answers to the following questions:

1. Can valid quantitative risk assessments be performed for these color additives?

2. Does the available information support the data analysis and risk assessments that have been performed and are before the agency?

X. Report of the Color Additives Scientific Review Panel

The panel evaluated the possibility of performing a scientifically valid carcinogenic risk assessment on D&C Orange No. 17 for externally applied drug and cosmetic uses. The panel did not consider risk assessments for other toxic endpoints—indeed, it was not necessary to do so because no safety concerns other than carcinogenicity have been associated with the external uses of D&C Orange No. 17. The panel's report contains a discussion on the assumptions that must be made in conducting a risk assessment and the uncertainties that are associated with such assumptions. The report is supported by several recent government agency efforts directed at developing a consensus of risk assessment: (1) The National Academy of Sciences Report on Risk Assessment; (2) The Office of Science and Technology Policy Document on Chemical Carcinogenesis; and (3) The Executive Committee, Coordinating Committee on Environmental and Related Programs Report on Risk Assessment.

The report contains a scientific introduction section for the major topics being discussed as well as a section on the general assumptions used in risk assessment of colors. The report discusses the risk assessments for each of the color additives by discussing major topics for each and the color additive-specific assumptions used, with the

focus on the risk under practical conditions of use. Each chapter also contains a risk characterization section which discusses the risk assessment of the individual color additive.

In its report, the panel critically reviewed the risk assessments submitted by CTFA. This included a detailed examination of the risk assessment methodology used by CTFA. In a summary chapter of the report (Chapter 9) the Panel stated that:

> In order to obtain a better perspective on the very complex and multifaceted problem of assessing exposure and toxic effect of the dyes, it was imperative to search for the many obvious or hidden, explicitly stated or implied assumptions associated with risk assessment of the dyes. In dissecting the presented problem into the smallest possible components, for which separate solutions might be formed, the Panel opted for starting with formulating the assumptions according to CTFA's line of reasoning (it should be emphasized, however, that CTFA made these assumptions to, presumably, derive a conservative risk estimate, while not necessarily supporting them). This was followed by a careful analysis of the validity of the statements, the possible alternatives to dealing with the gaps in knowledge and lack of information, and the quantitative assessment of the impact of the assumption on the magnitude of the risk of cancer, assuming that the dyes do pose such a risk to humans.
>
> While evaluating the many kinds of uncertainties in hazard identification, exposure assessment, and dose-response assessment, the Panel developed the view that, rather than limiting its role to analyzing CTFA's lines of reasoning, it attempt to use its analysis to generate modified risk estimates. This includes an estimate of the absorbed dose based on

more "reasonable" assumptions than those used in the CTFA assessments.

In the risk characterization section in the various dye chapters in the report, the panel compared the 90th percentile and the average usage (based on reasonable estimates). For the purpose of presenting the panel's assessment of the numerous assessments used in the CTFA risk assessments, the agency has summarized that portion of the panel's report which discusses the assumptions and the associated uncertainties. The summary below deals with assumptions which are relevant to all color additives reviewed by the panel.

A. *The Panel's Assumptions Used in Hazard Identification*

The panel generally accepted the assumptions used in the CTFA risk assessments largely because there seem to be no alternatives with higher degree of validity for the uncertainties involved and because they are consistent with what the panel understood FDA's policy to be. The panel believed the assumptions it relied upon to be conserative, i.e., are more likely to overestimate rather than underestimate the true risk.

The panel's assumptions concerning hazard identification were:

1. Because all six dyes of concern are animal carcinogens in some assay, they are suspect human carcinogens. (The panel made no evaluation of the weight-of-evidence for human carcinogenicity from the animal test results.)

2. Orally administered or ingested dyes are equally well absorbed in animals and humans, regardless of the test concentration of the dye and of the vehicle used.

3. Studies involving high doses of a compound under test are appropriate for low-dose extrapolation.

B. *The Panel's Assumptions Used in Exposure Assessment*

The panel's general assumptions regarding exposure assessments were:

1. The dyes are equally absorbed in rodents and man.

2. Dyes which penetrate the skin are as effective in evoking a carcinogenic response as if ingested.

3. For each dye, exposure is for 60 years (in contrast to CTFA's use of 70 years) and risk is not influenced by age at exposure. This results in a correction factor of 6/7.

4. An arbitrary value should be used to reflect the fact that cosmetic products contain other dyes than those of concern (or no dyes at all). Compared to the CTFA estimate, this results in a correction factor of 0.5.

5. Based on data for D&C Red No. 19 only, the average concentration of all dyes in commercial products is 25 percent of the highest concentration allowed. Compared to the CTFA estimate, this results in a correction factor of 0.25.

6. The skin model used for the skin absorption studies is appropriate for assessing the exposure to absorbed dye. Although the model is likely to overestimate the risk for products applied to the facial skin (skin penetration rates are likely to vary for different areas of the body), the model may underestimate the real absorption rate by a factor of 3.

7. In interpreting the results of the in vitro study on the absorption rates over time, the true absorption rate equals the steady state rate. Where the test did not reveal a steady state, twice the maximum rate at the end of 3 days approximates the true absorption rate.

8. Both types of CTFA surveys of the frequency of the use of dye containing products overestimate the frequency among the general population.

9. The absorbed amount of dye per day can be estimated by multiplying the amount of dye per day available for absorption by an absorption rate constant, as estimated from the in vitro tests. There is insufficient information, however, to calculate a better, less conservative estimate.

10. For each dye, the total exposure is the sum of exposures to all products containing the same dye.

11. The amount of dye-containing product per application is approximately 5 to 10 milligrams per square centimeter.

12. With the exception of nail products, the composition of the vehicle used in the commercial products does not affect the absorption rate assessed with the in vitro skin model. There is insufficient information to generate a best estimate of the absorption rate for each kind of commercial vehicle.

13. In an appropriate vehicle, there is no difference in absorption rate between a primary dye and its lake.

14. Based upon consideration of the structure and toxicity of actual impurities found in certified lots, the skin penetrance rates of subsidiary colors are not likely to be significantly different from that of the principal constituent. The skin penetrance rates of the other substances of concern (e.g., residual starting materials) have, at most, an effect of multiplying the risk by 1.2. This results in a correction of CTFA's estimate of the exposure by a factor of 1.2.

The panel's product-specific assumptions regarding exposure assessments were:

1. The absorption rate for hair cosmetics is 1.2 percent of the applied amount. This results in a correction of CTFA's estimate by a factor of 0.6.

2. No absorption occurs from dyes in nail products (CTFA assumed that 1 percent of the applied amount will penetrate the skin).

3. For bathwater products, 2 percent of the applied amount reaches the skin.

4. For wash-off products (including bathwater products), there is an absorption of 25 percent (CTFA assumed an absorption of 50 percent and excluded bathwater products from this consideration). This results in a correction of CTFA's estimate by a factor of 2.

5. For products other than wash-off products, there is an absorption of 50 percent (CTFA assumed an absorption of 100 percent). This results in a correction of CTFA's estimate by a factor of 2.

C. The Panel's Assumptions Used in Dose-Response Assessment

1. In test animals, 50 percent of orally administered dyes are absorbed from oral studies and the carcinogenic response is caused by this absorbed portion. This results in a correction of CTFA's estimate by a factor of 2.

2. On a milligram per kilogram body weight basis, dose levels used in animal tests have the same quantitative effect on the cancer incidence in humans. There is insufficient information for assessing the best estimate of the correct dose unit for use in extrapolating animal risk to human risk of cancer.

3. The average body weight of an adult woman is 53 kilograms.

4. The linearized multistage model reflects the true relationship between dose and response. The linearized multistage model may offer no added protection, however, in the convex portion of the dose-response curve. Low-dose linearity may overestimate the risk by several orders of magnitude if low-dose linearity is not present.

5. The most sensitive animal tumor data should be used to extrapolate risk from animal data to humans.

D. The Impact of the Panel's Assumptions on CTFA's Risk Estimate

In the chapters of the report concerning specific dyes, the panel applied the foregoing product- and dye-specific assumptions and correction factors to the usage data contained in the CTFA risk assessments. The panel also applied these assumptions to the survey estimates of 90th percentile exposure (the Risk/90 values) and "reasonable" estimates of exposure (Risk/Rea), thereby deriving revised risk estimates.

The impact on CTFA's risk assessment of the panel's general, quantifiable assumptions concerning exposure and dose-response are:

1. For skin absorption, a correction factor of 0.8 times the CTFA estimate (6/7x0.5x0.25x3x1.2x2).

2. For incidental ingestion of lip products, a correction factor of 6/7 times the CTFA estimate (a number of factors relevant only to skin absorption or not relevant to lipstick products do not apply).

3. At low dose levels, the risk of cancer, as computed with the linearized multistage risk model, is directly proportional to the dose levels.

The panel concluded that the correction factor of 0.8 for skin absorption is inconsequential when compared to the uncertainties in the assumptions that are difficult to quantify. The panel cautioned that the correction factor for skin absorption does not mean that the risk estimate is precise within 20 percent of the actual human risk. On the contrary, the figure merely represents the fact that, for the various quantifiable assumptions, underestimations and overestimations of risk in the CTFA estimates basically cancel out.

The panel also noted that many of the assumptions are not quantifiable. The panel, following prudent public health policy, stated that it accepted assumptions which are likely to overestimate rather than underestimate risk

in the cases difficult to quantify and is of the opinion that the human risk in the risk estimates it made is more likely to be over- rather than under-estimated.

E. Specific Assumptions

The panel in its review of risk assessment for D&C Orange No. 17 evaluated a number of CTFA's specific assumptions relevant to the color. The assumptions and the panel's comments are as follows:

1. CTFA assumed that for creams and oils the absorption rate is 0.01 percent per day.

The panel stated that the skin test revealed rates of 0.003 to 0.007 percent of the applied amount per 24 hours, implying an overestimation of the absorption by a factor of 2. The panel recognized that the real factor is unknown because it is not clear whether the rates refer to a maximum rate or a steady state rate.

2. CTFA assumed that the absorption rate for D&C Orange No. 17 in talc is 0.001 percent per day of the amount applied.

The panel stated that CTFA mentioned 0.001 percent absorption in its text, but printed 0.00009 percent in Table 6, which referenced Table 2 in Franz's report. The latter uses the value 0.001 percent. The panel used 0.001 percent.

3. CTFA assumed that the use of Volpo 20 in the receptor of the Franz cell will not significantly alter the skin penetration.

Based on its review of these color specific assumptions, the panel utilized the following assumptions in risk characterization:

(a) For creams and oils, the skin absorption rate is 0.005 percent per day of the amount applied, which is half the rate assumed by CTFA.

(b) For talc formulations, the skin absorption rate is 0.001 percent per day of the amount applied. This is in agreement with the rate assumed by CTFA.

(c) The low skin absorption rate of D&C Orange No. 17 is unlikely to be caused by the insolubility of the dye in the receptor phase. Replacing the usual saline receptor phase by one containing Volpo 20 did not result in increased dye penetration.

The panel also utilized the following specific assumptions in risk characterization:

(a) For nail products, the absorption of dyes is assumed to be zero, as compared to CTFA's assumption that no dye will be absorbed through the nail but that during application 1 percent of the dye may reach the skin or cuticle, where it will be available for absorption at the usual 1 percent rate.

(b) For products other than "wash-off" products, it is assumed that not more than 50 percent of the amount applied will stay available for absorption. CTFA assumed that the applied amount equaled the available amount.

F. The Panel's Interpretation of the Long-Term Studies

Prior to revising CTFA's risk estimates, the panel evaluated the available long-term studies of D&C Orange No. 17 in laboratory animals. The panel agreed with FDA that the 1.0 percent dosage level of D&C Orange No. 17 feeding study in rats was adequate and well-controlled and resulted in a statistically significant increase in the incidence of liver tumors (hepatocellular adenoma and carcinoma) in female rats as compared to controls.

In the case of D&C Orange No. 17, as with all the color additives it reviewed, the panel did not evaluate the weight-of-evidence for carcinogenicity to humans. Rather, the panel accepted as FDA's policy that any chemical

shown to induce cancer even in only one strain, gender, and species, at one dose in one experiment, is an animal carcinogen. In light of the fact that D&C Orange No. 17 is an animal carcinogen by FDA's standards, the panel considered that there was an appropriate empirical basis for estimating the possible cancer risks to man presented by the external uses of D&C Orange No. 17.

The panel reached this conclusion even though in its view the information from the D&C Orange No. 17 feeding study in mice does not provide definitive evidence that the additive is a carcinogen in mice. The panel found the mouse study to be well-controlled but considered the observed increase in liver tumors in the high-dose male mice to be equivocal. Nevertheless, the panel did prepare revised risk estimates based on the data from the mouse study.

G. Revised Risk Estimates

The panel's final step in evaluating the adequacy of CTFA's risk estimates on the external uses of D&C Orange No. 17 was to determine the total amount of the dye absorbed per day. In light of the fact that CTFA's information on the usage frequency that indicated that D&C Orange No. 17 was present in four different groups of products, the panel calculated that amount to be:

0.00189 microgram per day as an average of the prospective survey;

0.00635 microgram per day as the upper 90th percentile of the prospective survey;

0.00367 microgram per day as an average of the retrospective survey; and

0.007 microgram per day as the upper 90th percentile of the retrospective survey.

The comparable amounts calculated according to the CTFA assumptions are the upper 90th percentiles 0.0208

microgram per day (prospective survey) and 0.01542 microgram per day (retrospective survey). The panel believed that the prospective survey yielded less biased usage frequencies. Calculation of the resulting cancer risk estimates was, therefore, based on dose estimates based on the survey. At these very low dose levels, the dose-response curve is linear, meaning that the risk is directly proportional to the dose. The panel's revised estimates are based on 53 kilograms as a lifetime weight average for women, and include the panel's general correction factor of 0.8.

The panel's revised risk estimates are as follows:

	Risk (CTFA/90)*	Risk/90	Risk/Rea
Rat	2.1×10^{-10}	5.1×10^{-11}	1.5×10^{-11}
Mouse	0.7×10^{-10}	1.7×10^{-11}	0.5×10^{-11}

* Note that CTFA does not give an average exposure estimate for D&C Orange No. 17.

Risk(CTFA/90) is the CTFA risk estimate at the upper 90th percentile of exposure.

Risk/90 is the risk estimate based on the panel's calculation at the 90th percentile of exposure.

Risk(REA) is the risk estimate based on the panel's calculation of a more reasonable estimate of exposure.

The above risk estimates are based on the reasonable estimates of exposure, whenever the panel believed that it was possible to make such an estimate. In situations where available data would allow for a choice between "degrees of reasonable estimate," the panel consistently selected the estimate associated with the higher risk.

H. The Panel's Conclusion

The panel concluded that the animal studies were properly controlled except for a lack of data on the purity of the pigment (subsidiary color) or on the levels of impurities, at least one (2,4-dinitrobenzeneamine) of which

is a strong mutagen. In response to the agency's concerns regarding whether the available data and information adequately characterized the risk presented by exposure to possible impurities, the panel concluded that the level of impurities may have an impact on risk assessment only if the degree of potency of the impurities is greater, by several orders of magnitude, than the degree of potency of the pigment. Based on the strong mutagenicity of D&C Orange No. 17 without activation in several strains, the mutagenicity of the azo reduction product, and the reported mutagenicity of 2,4-dinotrobenzeneamine with or without activation, the panel concluded that it is unlikely that the carcinogenic "potency" differs from the parent compound by several orders of magnitude, and the general assumption concerning the likelihood that impurities would have no effect on the risk assessment is even more likely for this color additive.

XI. FDA's Decision to Permanently List D&C Orange No. 17

A. Reliance on Risk Estimation Techniques

The data and information regarding the safety of D&C Orange No. 17 support FDA's conclusion that the substance induces cancer when tested in laboratory animals. The data and information, however, do not support any other finding of toxicity.

In the past, because the data and information show that D&C Orange No. 17 is a carcinogen when ingested by laboratory animals, FDA in all likelihood would have terminated the provisional listing and denied CTFA's petition for the externally applied uses of D&C Orange No. 17 without any further discussion. In the present instance, however, CTFA has presented arguments that this color additive can be regulated for safe use in externally applied drugs and cosmetics. The arguments CTFA has presented are based on the premise that a

determination of safety may be based on risk assessment techniques. FDA agrees that risk estimation methods are frequently helpful in evaluating the safety of carcinogenic substances. It was for these reasons that the agency requested the panel to determine whether the data and information available concerning D&C Orange No. 17 provided an adequate basis from which to make reliable risk estimations.

FDA agrees with the panel that CTFA's risk estimates on the use of D&C Orange No. 17 in externally applied drugs and cosmetics, as modified in the panel's report, represent a reliable upper bound risk and that those risk estimates can be used to evaluate the proposed external uses of D&C Orange No. 17. FDA also agrees, for the purpose of conducting a risk assessment, with the panel's resolution of the agency's concerns regarding the possible toxicity of impurities in the color additive.

B. The Safety of D&C Orange No. 17

Under section 706(b)(4) of the act (21 U.S.C. 376(b)(4)), the so-called general safety clause of the statute, FDA cannot approve a color additive for a particular use unless the data presented to FDA establish that the color additive is safe for that use. Although what is meant by safe is not explained in the general safety provision, the legislative history of the act makes clear that safety requires proof to a reasonable certainty that no harm will result from the proposed use of an additive. Because FDA considers D&C Orange No. 17 to be a carcinogen when ingested by laboratory animals, as discussed above, the Delaney Clause (section 706(b)(5)(B)(i) of the act) is applicable. A strictly literal application of the Delaney Clause would prohibit FDA from finding that D&C Orange No. 17 is safe and, therefore, prohibit FDA from permanently listing the color for externally applied uses in drugs and cosmetics. However, as seen from CTFA's and the panel's risk estimates, the calculated risk for

these uses of D&C Orange No. 17 is extremely low. In fact, the level is three to four orders of magnitude lower than that level of risk which the agency accepts in other areas concerning carcinogens; for example, its procedures and criteria for permitting carcinogenic food additive residues in animal tissues under section 512(d)(1)(H) of the act, the DES proviso to the Delaney Clause (21 U.S.C. 360b(d)(1)(H)) (see 50 FR 45530, 45541; October 31, 1985; FDA refers to these procedures and criteria as the sensitivity of the method or SOM procedures). With such a negligible risk, there is no gain to the public and the statutory purpose is not implemented or served by an agency action delisting the substance.

Under these circumstances, FDA concludes that it should not interpret the Delaney Clause to require a ban on this use of D&C Orange No. 17. Therefore, FDA has decided to exercise its inherent authority under the *de minimis* doctrine and concludes that the Delaney Clause does not require a ban in the case of the externally applied uses of D&C Orange No. 17. Because there are no other safety problems with this use of D&C Orange No. 17, FDA finds that the externally applied uses are safe.

C. CTFA's Legal Arguments

In its April 15, 1983, submission, CTFA argued that the applicable statutory authority under the act and judicial precedent authorize FDA to apply a *de minimis* interpretation of the Delaney Clause for a carcinogenic color additive that presents an insignificant risk of cancer. CTFA also argued that the Delaney Clause does not apply to the external uses of D&C Orange No. 17 because the tests on D&C Orange No. 17 are not appropriate for the evaluation of the substance.

FDA agrees with the former position and in the following section of this notice discusses the applicability of the *de minimis* doctrine to D&C Orange No. 17. The

agency, however, disagrees with CTFA's latter argument, one that draws heavily on the agency's decision to list the color additive lead acetate (45 FR 72112, October 31, 1980; 46 FR 15500, March 6, 1981). CTFA's studies show that a portion of the radiolabeled material in the D&C Orange No. 17 used for percutaneous study penetrated the skin and entered the circulatory system. Under these circumstances, in the absence of any metabolic or other data suggesting that ingestion studies are inapplicable, ingestion studies are appropriate as a basis for risk assessment of the external use of D&C Orange No. 17.

Moreover, FDA's decision concerning lead acetate was based upon the unusual combination of scientific facts, peculiar to the use of lead acetate in hair dyes, which the agency recognized "will rarely, if ever, be presented again in this context" (45 FR 72112, 72115; October 31, 1980). Similar facts do not exist in the case of D&C Orange No. 17. For example, a key factor that influenced FDA's judgment that the Delaney Clause just did not apply to lead acetate was the fact that a background level of lead is always present in the blood of humans, a background level much greater than the possible increase in lead burden that would result from the use of lead acetate in hair dyes. There is, of course, no background level of D&C Orange No. 17 in humans. The agency believes that the tests on D&C Orange No. 17 are appropriate for an evaluation of the substance under the Delaney Clause.

D. The de Minimis Doctrine and Its Applicability to D&C Orange No. 17

Two conditions must apply to justify an agency's exercise of its authority to interpret a legal requirement as not requiring action in *de minimis* situations. First, it must be consistent with the legislative design for the agency to find that a situation is trivial and, there-

fore, one that need not be regulated. *Alabama Power Co.* v. *Costle*, 636 F.2d 333, 360 (DC Cir. 1979). Second, it must be clear that the situation is in fact trivial, and that no real benefit will flow from regulating the particular situation. *Environmental Defense Fund* v. *Environmental Protection Agency*, 636 F.2d 1267, 1283-1284 (DC Cir. 1980). Both conditions apply here.

1. The establishment of a *de minimis* exception to the Delaney Clause is consistent with the legislative design.

In *Alabama Power* v. *Costle*, supra, the court stated that the implication of *de minimis* authority is consistent with most statutes. The court stated that unless Congress has been extraordinarily rigid, there is likely a basis for an implication of such authority. *Id.* at 360-361. That Congress was not so rigid as to preclude the implication of *de minimis* authority under the Delaney Clause is evidenced both by the stated congressional intent in enacting the Delaney Clause and by the stated purpose of this provision.

The clearest statement of the congressional intent for the Delaney Clause is in the legislative history of the Color Additive Amendments of 1960. The Senate considered that the calculation of risk would permit interpretation of the Delaney Clause to allow color additives producing a negligible risk. This is clear from a colloquy on the Senate floor initiated by Senator Jacob Javits in debate on his motion to reconsider the vote to approve the Color Additive Amendments. Senator Javits, focusing on the Delaney Clause, made the record clear in discussion with Republican leader Senator Dirksen and committee chairman Senator Hill that the Senate had agreed to pass the Color Additive Amendments with the Delaney Clause based upon its understanding that the authority conferred by that clause "should be used and applied within the 'rule of reason.'" 106 Congressional

Record 15381 (July 1, 1960).[1] Both Senator Dirksen and Senator Hill agreed that the "rule of reason" was to be applied in interpreting the Delaney Clause. *Id.* On that basis, Senator Javits did not pursue his motion to reconsider.

The term "rule of reason" was taken from a report to the President from the President's Science Advisory Committee and from the Departments of Agriculture and of Health, Education, and Welfare (the predecessor of the Department of Health and Human Services) that analyzed the effect of the Delaney Clause that is applicable to food additives. That report defines the "rule of reason" as meaning that: "Every statute must be interpreted in the light of reason and common understanding to reach the results intended by the legislature." 106 Congressional Record 15380. The report stated its conclusion that "an area of administrative discretion based on the rule of reason is unavoidable if the clause is to be workable." 106 Congressional Record 15381.

This report on implementation of the food additive provision relied upon by the Senators as illustrating their understanding of the types of circumstances in which the "rule of reason" would appropriately be applied, accurately predicted the advent of the science of risk assessment. The report stated that: "From the experience obtained in animal experiments and study of humans who have been exposed to carcinogens in the course of their work the panel believes that the probability of cancer induction from a particular carcinogen in minute

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[1] More recently, Senator Javits reviewed this discussion. On July 10, 1985, he sent Margaret Heckler, Secretary of the Department of Health and Human Services, a letter stating that his views had not changed since 1960. He stated that it was his continuing understanding that the rule of reason "would dictate that where the danger to the public is negligible in using products with such color additives, then use should not be prohibited." A copy of Senator Javits' letter to Secretary Heckler is included in the record of this rulemaking.

doses may be eventually assessed by weighing scientific evidence as it becomes available." 106 Congressional Record 15380-15381.

Thus, the Senate agreed to adopt the color additive Delaney Clause only with the understanding that the clause would be administered with "a rule of reason," premised on the expectation that scientists would be able to determine the "probability of cancer induction." Thus, far from having been "extraordinarily rigid," Congress clearly contemplated that those administering the Delaney Clause would have discretion to implement that provision in a reasonable way.[2]

The purpose of the Delaney Clause in section 706 of the act is, after all, to protect the public from the possibility of increasing cancer risks through the use of color additives. It does not advance this purpose to prohibit uses that present a risk that is, for all practical purposes, zero. Congress recognized this fact in warning FDA not to "go overboard" in applying the Delaney Clause. 106 Congressional Record 15381. Thus, it is not inconsistent with the Delaney Clause to permit some uses of a carcinogenic color additive when those uses are shown to present a potential carcinogenic risk that is so trivial, based on extremely conservative statistical analyses, as to be the functional equivalent of no risk at all.

This interpretation of the Delaney Clause finds support in recent case law. In *Monsanto* v. *Kennedy*, 613 F.2d 947 (DC Cir. 1979), the court held that not all chemicals that become components of food need be considered food additives. The court stated that FDA has

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[2] This grant of discretion is not inconsistent with the fact that Congress clearly intended to prevent the imposition of a tolerance for a carcinogen. Where the probability of harm is so small as to be of no practical significance, it is reasonable and appropriate to apply the *"de minimis"* concept. And, doing so does not in any way reflect an intent to set a tolerance.

the authority to ignore a chemical that migrates from plastic packaging material into beverages if the amount of the chemical that migrates is *de minimis*. The court made that statement after it had found that some amount of the chemical in question would become a component of food by migration from packaging material—thus undeniably satisfying a literal reading of the statute. The court was concerned that the Commissioner may have reached his determination in the belief "that he was constrained to apply the strictly literal terms of the statute irrespective of the public health and safety considerations." 613 F.2d at 954. Accordingly, the court emphasized that there is "latitude inherent in the statutory scheme to avoid literal application of the statutory definition of 'food additive' in those *de minimis* situations that, in the informed judgment of the Commissioner, clearly present no public health or safety concerns." *Id.* Thus, the *Monsanto* decision is important to the agency's present action even though that case involved the definition of "food additive" and not the application of the Delaney Clause, and even though FDA, when it issued the order that was ultimately reviewed by the court, had not made a final determination as to the carcinogenicity of the chemical at issue, acrylonitrile monomer.

The court also held in *Monsanto* that the "*de minimis*" concept, applied to the threshold "food additive" definition, could be utilized to allow the marketing of a substance that presents no real public health risk. See 613 F.2d at 955-956. Thus, the court's decision in *Monsanto* has the practical effect of shielding substances that present effectively no carcinogenic risk from the Delaney Clause. Although the court did not explicitly interpret the Delaney Clause as inapplicable to such substances, the court presumably knew that if a carcinogenic chemical was disregarded as *de minimis* in relation to the food additive definition, the chemical would not be sub-

ject to the Delaney Clause, which applies only when that definition is met. Necessarily, therefore, the court regarded this consequence as legally warranted.

Moreover, in *Scott* v. *FDA*, 728 F.2d 322, 325 (6th Cir. 1984), the Sixth Circuit upheld the so-called constituents policy, whereby FDA may approve known carcinogens present in color additives as intermediaries or impurities present at levels too low to cause a response using conventional tests. Noting that FDA had determined the public health risk presented by D&C Green No. 5 was negligible, the court reasoned:

> * * * We find this determination by the *Monsanto* court persuasive and relevant to the particular facts of the instant case. We agree with the FDA's conclusion that since it "has discretion to find that low level migration into food of substances in indirect additives is so insignificant as to present no public health or safety concern * * * it can make a similar finding regarding a carcinogenic constituent or impurity that is present in a color additive" 47 FR 24280 (1982).

In addition to the foregoing precedents, the state of scientific knowledge about cancer when the Delaney Clause was passed also supports the implication of *de minimis* authority under the Delaney Clause and the fact that the provision could not possibly have been meant to be "extraordinarily rigid." In 1958, there were only four substances that were known to induce cancer in humans: soot, radiation, tobacco smoke, and *beta*-naphthylamine (Ref. 13). Only 20 years later, scientists had identified 37 human carcinogens and over 500 animal carcinogens (Ref. 13). This growth in knowledge is in part the result of an enormous increase in carcinogenicity testing in laboratory animals. As testing increases, more and more substances are found to induce cancer at some site in at least some strain or sex of laboratory animal. For example, of the 86 compounds

tested by the National Toxicology Program (NPT) and reported between July 1981 and July 1984, 50 percent were determined to induce some carcinogenic effect (Ref. 14). (It should be noted that many of the compounds tested by NPT were, prior to testing, suspected of being carcinogenic.) Furthermore, recent short- and long-term toxicity testing has shown that a large number of substances naturally present in food are mutagenic or carcinogenic (Ref. 15).

With the advent of sensitive chemical analytical methodologies, scientists have been able to find carcinogens throughout the food supply in extremely small quantities. In 1958, the available methodologies were far less sensitive than they are today. For example, as FDA stated in its 1979 SOM proposal, the sensitivity of the methodologies increased during the period between 1958 and 1978 by "between two and five orders of magnitude" (44 FR 17070, 17075; March 20, 1979). This improved sensitivity has allowed the detection of carcinogens in the parts per trillion level so that, as one scientist has reported, "today substances can be routinely measured at concentrations up to a million times less than was possible in 1958" (Ref. 13).

There is no indication that in 1958 Congress foresaw the likelihood that, within less than 30 years after the Delaney Clause was enacted, science would have progressed so far as to be able to document the widespread presence of trace amounts of proven carcinogens in food. There is no indication that Congress anticipated the extent to which substances, then regarded either as absent from foods or as noncarcinogenic on the basis of less adequate technology, would later prove to be carginogenic. In short, the scientific knowledge about carcinogens was much more limited in 1958 than it is today. The solution Congress decided upon in 1958 for handling added carcinogens, given that state of knowledge, was not extraordinarily rigid but was entirely reasonable, i.e., a

few substances, present at levels then detectable, would be banned; most food would be unaffected.

Under these circumstances, it would not be consistent with the legislative design for FDA today, to attempt to prohibit all added carcinogens from the food supply provided the risks presented by permitted levels are trivial. Permitting merely a *de minimis* level of risk from such carcinogens is not only sound regulatory policy but is also consistent with the underlying purpose of the Delaney Clause as enacted in 1958—the assurance that the food supply will be free from any meaningful risk of cancer presented by substances added to food.

For all the foregoing reasons, the agency concludes that it is consistent with the Delaney Clause to permit uses of a carcinogenic color additive when those uses are shown to present a carcinogenic risk that is so trivial, based on extremely conservative statistical analyses, as to be the functional equivalent of no risk at all.

2. The risk from the use of D&C Orange No. 17 in externally applied drugs and cosmetics is, in fact, so trivial as to be effectively no risk.

According to the panel's revised risk estimates, the highest lifetime level of risk presented by the external uses of D&C Orange No. 17 is 1 in 19 billion, i.e., 5.1×10^{-11}. This is not an actuarial risk. An actuarial risk is the risk determined by the actual incidence of an event. In contrast, the computed risk is a projection based on certain conservative assumptions that do not understate risk. The assumptions that were relied upon in this computation have been stated previously in the document based on the panel's computations. The risk from the use of D&C Orange No. 17 in externally applied drugs and cosmetics will not exceed 1 in 19 billion and is likely to be somewhere between that level and zero. The 1 in 19 billion level represents a 1 in 19 billion increase in risk over the normal risk of cancer in a

lifetime—not annual—risk. FDA emphasizes that the 1 in 19 billion level of risk does not mean that 1 in every 19 billion people will contract cancer as a result. Rather, in all likelihood, no one will contract cancer as a result of this exposure.

In light of the level of risk presented by the external uses of D&C Orange No. 17, FDA finds that the uses are safe, that they impose no additional risk of cancer to the public, and that any risk they may present is of no public health consequence. It is in just these circumstances, where there is no meaningful increase in public health protection from applying the strict, literal terms of a legal standard, that the courts have found the *de minimis* doctrine to be applicable. For example, the court in *Monsanto* equated "*de minimis*" with a finding that migration of an indirect food additive is "insignificant" (613 F.2d at 947) in a context where the court clearly recognized that the real question was the toxicity of a particular level of migration.

Furthermore, FDA and other regulatory agencies have, in the past, found higher risks than those presented by D&C Orange No. 17 to be permissible. For example, in the ongoing SOM rulemaking proceeding, FDA has proposed that an assay method sufficient to detect a carcinogenic residue posing a calculated upper bound risk of 1 in 1 million is appropriate because such a level imposes no adidtional risk of cancer to the public (see 44 FR 17070, 17093; March 20, 1979). The agency has concluded that as a result of this use of the 1 in 1 million level of risk as far as can be determined in all probability, no one will contract cancer from admittedly carcinogenic residues in edible animal tissue. (See 50 FR 45530, 45541; October 31, 1985.)

In several proceedings involving the agency's policy for carcinogenic impurities in food and color additives, FDA has also found that a risk on the order of a 1 in 1 million lifetime risk is low enough to be considered safe

within the meaning of the general safety clause. See, for example, the administrative record compiled in the rulemaking on D&C Green No. 6 (47 FR 14138; April 2, 1982).

Furthermore, in a notice published in the Federal Register of December 18, 1985 (50 FR 51551), the agency proposed that methylene chloride when used to decaffeinate coffee is safe, in light of the fact that the potential risk posed by permitted levels of methylene chloride residue in coffee does not exceed 1 in 1 million. In that notice, the agency also suggested that the lifetime risk for this use of methylene chloride to decaffeinate coffee is *de minimis*.

Other Federal agencies have also used a 1 in 1 million level as a basis for regulatory decisionmaking permitting human exposure to carcinogens (Ref. 16). In fact, they have sometimes made regulatory decisions that have allowed a cancer risk greater than 1 in 1 million. The Occupational Safety and Health Administration (OSHA), for example, has focused on its regulatory efforts on risks in the workplace that are much higher than 1 in 1 million lifetime level of risk.

For example, under the Occupational Safety and Health Act (OSH Act) (29 U.S.C. 651 et seq.), OSHA issues health standards for the workplace. Before issuing a standard, OSHA must make a formal showing of "significant risk from exposure." Accordingly, OSHA uses quantitative risk assessment to compare the magnitude of risk presented by the various possible levels of exposure to a substance before establishing a permissible exposure limit. In the Federal Register of January 14, 1983 (48 FR 1864), OSHA established a new permissible exposure limit for inorganic arsenic after determining the risk of lung cancer death associated with such a level would be 8 cases per 1,000 workers exposed over a working lifetime. The standard was upheld by the Ninth Circuit Court of Appeals in *ASARCO* v. *OSHA*, 746 F.2d

483 (9th Cir. 1984). In a similar action in the Federal Register of June 22, 1984 (49 FR 25734), OSHA published a final rule establishing a new permissible exposure limit for ethylene oxide. The new 1 part per million permissible exposure limit represented a risk of 12 to 23 excess deaths per 10,000 workers exposed over a working lifetime.

The Environmental Protection Agency (EPA) in recent years has also relied upon the 1 in 1 million lifetime level as a reasonable criterion for separating high risk problems from low risk problems presented by the wide ranging environmental contaminants EPA must regulate. In the Federal Register of November 23, 1984 (49 FR 46294), EPA proposed guidelines for carcinogen risk assessment. The proposal outlined a procedure for characterizing substances based on the experimental weight of evidence of carcinogenicity. For those compounds classified as known or probable human carcinogens, EPA set the 1 in 1 million risk level as the "point of departure" for determining what level of a carcinogen may cause concern.

For example, under the Safe Drinking Water Act (42 U.S.C. 300f et seq.), EPA sets drinking water standards that contain maximum contaminant levels for toxicants, including carcinogens. Maximum contaminant levels for carcinogens that have been promulgated or proposed to date by EPA generally fall into lifetime risk ranges of 1 in 10,000 to 1 in 1 million (Ref. 17). Similarly, EPA recently proposed to establish the 1 in 1 million level as the "point of departure" in determining the level of control for all known and possible carcinogenic constituents compounds resulting from hazardous waste contamination (51 FR 1602, 1635; January 14, 1986). As an alternative, EPA proposed to consider estimates of population in determining the appropriate level of control for each constituent. Thus, if a very large number of people is believed to be potentially exposed to a very potent carcinogenic constituent released from con-

taminated land disposal units, EPA could decrease the level of risk to as low as 1 in 10 million. If the size of the potentially exposed population is not large, the "point of departure" would remain at the 1 in 1 million level. However, if a small number of people was believed to be exposed to the contaminant, such that the incidence of cancer would be expected to be small from the exposure, EPA would consider increasing the acceptable risk level to 1 in 100,000 or 1 in 10,000.

Although comparisons between the safety decisions made by OSHA and EPA with those made by the FDA must be tempered by the fact that the decisions are made under different statutory frameworks, the decisions support the consensus proposition that a lifetime level of 1 in 1 million presents an extremely small risk.

Furthermore, FDA's conclusion that a 1 in 1 million lifetime level represents an insignificant level of risk has not been arrived at hastily. For example, when it first proposed the SOM procedures and criteria on July 19, 1973 (38 FR 19226), the agency stated that an acceptable level of risk for carcinogenic residues in edible animal tissues would be 1 in 100 million. In the Federal Register of February 22, 1977 (42 FR 10412), the agency concluded that the 1 in 100 million level was unnecessarily conservative in light of the numerous conservatisms implicit in risk assessment and because the level provided only a minor incremental increase in the degree of confidence presented by the higher 1 in 1 million level. The agency concluded that the 1 in 1 million level constituted a risk level that one could properly consider to present an insignificant public health concern (see also 44 FR 17070; March 20, 1979). In the most recent Federal Register document concerning the SOM rulemaking (50 FR 45530; October 31, 1985), the agency explained that it considered raising the level yet another order of magnitude to 1 in 100,000 but chose not to do so. FDA reasoned that in recent years the 1 in 1 million level has

become a benchmark in the evaluation of the safety of carcinogenic compounds administered to food-producing animals.

Furthermore, the agency stated that there is currently widespread confidence that this level presents an insignificant risk of cancer. This point is underscored by the fact that every comment on the risk level aspect of the 1979 SOM proposal regarded the 1 in 1 million level as insignificant. In making the decision to retain the 1 in 1 million level for purposes of the SOM proceeding, FDA recognized explicitly that there may be a higher level of risk that is more appropriate to characterize as a "no residue" level, but that in light of the current uncertainties that accompany making a decision as to the most appropriate level of risk, the 1 in 1 million level was the most reasonable and defensible choice (50 FR 45542).

The level of risk presented by the external uses of D&C Orange No. 17 is extremely low. In relation to other risks regulated by FDA and other Federal agencies, the risk presented by the external uses of D&C Orange No. 17 is, indeed, trivial.

XII. Conclusion

Based on the foregoing, FDA concludes that the risk of cancer from the use of D&C Orange No. 17 in externally applied drugs and cosmetics is so low (1 in 19 billion) as to be effectively no risk, and that there would be no benefit to the public from prohibiting these uses of the color additive. Further, for the same reasons and because the available information indicates no other safety questions regarding the use of D&C Orange No. 17 in externally applied drugs and cosmetics, FDA concludes that the externally applied uses of D&C Orange No. 17 are safe. The agency is amending Part 74 to permanently list D&C Orange No. 17 for such uses.

The agency is describing the color additive in this regulation according to current Chemical Abstracts Service

nomenclature, which differs somewhat from the nomenclature FDA previously used, and the agency is establishing new chemical specifications for the Part 74 listings that identify the color additive more precisely than those currently listed in 21 CFA 82.1267.

FDA is also modifying its regulations to conform them to the decisions announced in this document.

In accordance with § 71.15 (21 CFR 71.15), the petition and the documents that FDA considered and relied upon in reaching its decisions to approve the petition are available for inspection at the Center for Food Safety and Applied Nutrition (address above) by appointment with the information contact person listed above. As provided in § 71.15, the agency will delete from the documents any materials that are not available for public disclosure before making the documents available for inspection.

The agency has determined under 21 CFR 25.24(b)(3) (April 26, 1985; 50 FR 16636) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Executive Order 12291 and the Regulatory Flexibility Act (Pub. L. 96-354) do not apply to actions of this type.

XIII. References

The following information has been placed on file at the Dockets Management Branch (address above) and is available for review in that office between 9 a.m. and 4 p.m., Monday through Friday. The final toxicity study reports, the agency's toxicology evaluations of these studies, and other information relied upon by the agency in reaching its decision are also on file at the Dockets Management Branch for public review.

1. Sontag, J.M., N.P. Page, and U. Saffratti, "Guidelines for Carcinogen Bioassay in Small Ro-

dents," DHEW Publication No. (NIH) 76-801, p. 14, 1976.

2. International Expert Advisory Committee to the Nutrition Foundation, "The Relevance of Mouse Liver Hepatoma to Human Carcinogenic Risk," September 1983.

3. "Interagency Regulatory Liaison Group (1979) Scientific Bases for Identification of Potential Carcinogens and Estimation of Risks," *Journal of the National Cancer Institute*, 63:241-268, and Federal Register 44:131:39858-39879 (July 6, 1979).

4. Jackson, B.A., "Regulatory Interpretation of Proliferative Lesions of Rodent Liver," *FDA Bylines*, # 1 (January 1981).

5. Bureau of Foods' Cancer Assessment Committee Reports on Benzidine and Aniline, December 20, 1983.

6. Klaassen, C.D., "Absorption, Distribution and Excretion of Toxicants," Chapter 3 *in* "Toxicology, The Basic Science of Poisons," Casarett, L.J., and J. Doull (Eds.), Macmillan Pub. Co., Inc., New York, pp. 26-44, 1975.

7. "Report of the Color Additive Scientific Review Panel," September 1985.

8. Memorandum to File from W. Gary Flamm, "Environ Report."

9. Franz, T.J., "Percutaneous Absorption of D&C Orange No. 17 Through Human Skin in Vitro," March 25, 1983.

10. Letter from J. Schwing to N. Estrin, October 19, 1977.

11. Cancer Assessment Committee Memorandum of Conference, August 5, 1982.

12. Cancer Assessment Committee Memorandum of Conference, January 20, 1983.

13. Wilson, R., "Risks Caused By Low Levels of Pollution," *Yale Journal of Biology and Medicine*, 51:37, 48, 1978.

14. Haseman, J., et al., "Results From 86 Two-Year Carcinogenicity Studies Conducted by the National Toxicology Program," *Journal of Toxicology and Enviromental Health*, 14:621, 634, 1984.

15. Ames, B., "Dietary Carcinogens and Anticarcinogens," *Science*, 221:1256, September 23, 1983.

16. Milvy, P., "A General Guideline for Management of Risk from Carcinogens," *Risk Analysis*, 6:69, 1986.

17. Crouch, E., et al., "The Risks of Drinking Water," *Water Resources Research*, 19:1359, 1983.

XIV. Objections

Any person who will be adversely affected by this regulation may at any time on or before September 8, 1986, file with the Dockets Management Branch (address above) written objections thereto. Each objection shall be separately numbered, and each numbered objection shall specify with particularity the provisions of the regulation to which objection is made and the grounds for the objection. Each numbered objection on which a hearing is requested shall specifically so state. Failure to request a hearing for any particular objection shall constitute a waiver of the right to a hearing on that objection. Each numbered objection for which a hearing is requested shall include a detailed description and analysis of the specific factual information intended to be presented in support of the objection in the event that a hearing is held. Failure to include such a description and analysis for any particular objection shall constitute a waiver of the right to a hearing on the objection. Three copies of all

documents shall be submitted and shall be identified with the docket number found in brackets in the heading of this document. Any objections received in response to the regulation may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday. FDA will publish notice of the objections that the agency has received or lack thereof in the Federal Register.

List of Subjects

21 CFR Part 74

Color additives, Cosmetics, Drugs, Medical devices.

21 CFR Part 81

Color additives, Cosmetics, Drugs.

21 CFR Part 82

Color additives, Cosmetics, Drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, Parts 74, 81, and 82 are amended as follows:

PART 74—LISTING OF COLOR ADDITIVES SUBJECT TO CERTIFICATION

1. The authority citation for 21 CFR Part 74 is revised to read as follows:

> Authority: Secs. 701, 706, 52 Stat. 1055-1056 as amended, 74 Stat. 399-407 as amended (21 U.S.C. 371, 376); 21 CFR 5.10.

2. By adding new § 74.1267 to read as follows:

§ 74.1267 D&C Orange No. 17.

(a) *Identity.* (1) The color additive D&C Orange No. 17 is 1-[(2,4-dinitrophenyl)azo]-2-naphthalenol (CAS Reg. No. 3468-63-1). The color additive is manufactured by diazotization of 2,4-dinitrobenzeneamine in acid medium and coupling with 2-naphthalenol in acid medium.

(2) Color additive mixtures for use in externally applied drugs made with D&C Orange No. 17 may contain only those diluents that are suitable and that are listed in Part 73 of this chapter for use in color additive mixtures for coloring externally applied drugs.

(b) *Specifications.* D&C Orange No. 17 shall conform to the following specifications and shall be free from impurities other than those named to the extent that such impurities may be avoided by current good manufacturing practice:

Volatile matter (at 135° C.), not more than 1.5 percent.

Matter insoluble in toluene, not more than 1.5 percent.

2,4-Dinitrobenzeneamine, not more than 0.2 percent.

2-Naphthalenol, not more than 1.2 percent.

4-[(2,4-Dinitrophenyl)azo]-1-naphthalenol, not more than 0.3 percent.

1-[(4-Nitrophenyl)azo]-2-naphthalenol, not more than 0.3 percent.

Lead (as Pb), not more than 20 parts per million.

Arsenic (as As), not more than 3 parts per million.

Mercury (as Hg), not more than 1 part per million.

Total color as determined by spectroscopy, not less than 95 percent.

(c) *Uses and restrictions.* The color additive D&C Orange No. 17 may be safely used for coloring externally

applied drugs in amounts consistent with current good manufacturing practice.

(d) *Labeling.* The label of the color additive and any mixtures prepared therefrom intended solely or in part for coloring purposes shall conform to the requirements of § 70.25 of this chapter.

(e) *Certification.* All batches of D&C Orange No. 17 shall be certified in accordance with regulations in Part 80 of this chapter.

3. By adding new § 74.2267 to read as follows:

§ 74.2267 D&C Orange No. 17.

(a) *Identity and specifications.* The color additive D&C Orange No. 17 shall conform in identity and specifications to the requirements of § 74.1267(a)(1) and (b).

(b) *Uses and restrictions.* The color additive D&C Orange No. 17 may be safely used for coloring externally applied cosmetics in amounts consistent with current good manufacturing practice.

(c) *Labeling.* The label of the color additive and any mixtures prepared therefrom intended solely or in part for coloring purposes shall conform to the requirements of § 70.25 of this chapter.

(d) *Certification.* All batches of D&C Orange No. 17 shall be certified in accordance with regulations in Part 80 of this chapter.

PART 81—GENERAL SPECIFICATIONS AND GENERAL RESTRICTIONS FOR PROVISIONAL COLOR ADDITIVES FOR USE IN FOODS, DRUGS, AND COSMETICS

4. The authority citation for 21 CFR Part 81 continues to read as follows:

Authority: Secs. 701, 706, 52 Stat. 1055-1056 as amended, 74 Stat. 399-407 as amended (21 U.S.C.

371, 376); Title II, Pub. L. 86-618; sec. 203, 74 Stat. 404-407 (21 U.S.C. 376, note): 21 CFR 5.10.

§ 81.1 [Amended]

5. In § 81.1 *Provisional lists of color additives* by removing the entry for "D&C Orange No. 17" in paragraph (b).

§ 81.27 [Amended]

6. In § 81.27 *Conditions of provisional listing* by removing the entry for "D&C Orange No. 17" in paragraph (d).

PART 82—LISTING OF CERTIFIED PROVISIONALLY LISTED COLORS AND SPECIFICATIONS

7. The authority citation for 21 CFR Part 82 is revised to read as follows:

Authority: Secs. 701, 706, 52 Stat. 1055-1056 as amended, 74 Stat. 399-407 as amended (21 U.S.C. 371, 376); 21 CFR 5.10.

8. By revising § 82.1267 to read as follows:

§ 82.1267 D&C Orange No. 17.

The color additive D&C Orange No. 17 shall conform in identity and specifications to the requirements of § 74.1267(a)(1) and (b) of this chapter.

Dated: July 26, 1986.

Frank E. Young,

Commissioner of Food and Drugs.

APPENDIX C

21 CFR Parts 74, 81, and 82

[Docket No. 83C-0129]

Listing of D&C Red No. 19 For Use in Externally Applied Drugs and Cosmetics

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is permanently listing D&C Red. No. 19 as a color additive for use in externally applied drugs and cosmetics. FDA is taking this action because it has concluded that the use of this color additive in externally applied drugs and cosmetics is safe within the meaning of section 706 of the Federal Food, Drug, and Cosmetic Act. This action responds to a petition filed by the Cosmetic, Toiletry and Fragrance Association, Inc. (CTFA).

DATES: Effective September 9, 1986, except as to any provisions that may be staved by the filing of proper objections; objections by September 8, 1986 FDA will publish notice of the objections that the agency has received or lack thereof in the Federal Register.

ADDRESS: Written objections to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Gerad L. McCowin, Center for Food Safety and Applied Nutrition (HFF-330), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-472-5676.

SUPPLEMENTARY INFORMATION:

I. Introduction

In 1960, Congress passed the Color Additive Amendments (the amendments). In *Certified Color Mfg. Ass'n* v. *Mathews*, 543 F.2d 284, 286-287 (D.C. Cir. 1976), the United States Court of Appeals for the District of Columbia Circuit explained the purpose of this legislation:

> The Color Additive Amendments of 1960 reflect a Congressional and administrative response to the need in contemporary society for a scientifically and administratively sound basis for determining the safety of artificial color additives, widely used for coloring foods, drugs, and cosmetics. The Amendments reflect a general unwillingness to allow widespread use of such products in the absence of scientific information on the effect of these products on the human body. The previously used system had some glaring deficiencies, and the 1960 Amendments were designed to overcome them. * * * [Footnotes omitted.]

As amended, the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.) (the act) provides in section 706(a) (21 U.S.C. 376(a)) that a color additive will be deemed unsafe for use in food, drugs, cosmetics, and some medical devices unless FDA has issued a regulation permanently listing that color additive for its intended use (21 U.S.C. 376(a)). FDA will issue such a regulation only if it has been presented with data that establish with reasonable certainty that no harm will result from the use of the color additive. The burden of presenting such data is on the person who is seeking approval of the use of the additive.

In passing the amendments, Congress provided for the provisional listing of the color additives in use at that time, pending completion of the scientific investigations needed for a determination about the safety of these

additives (section 203(b) of the transitional provisions of the amendments, Title II, Pub. L. 86-618, 74 Stat. 404-407 (21 U.S.C. 376, note)). Section 81.1 (21 CFR 81.1) of the agency's color additive regulations enumerates those color additives that are still provisionally listed. Among them is D&C Red No. 19 for use in externally applied drugs and cosmetics.

II. Regulatory History

A. The Color Additives

The color additive D&C Red No. 19 has been in use for many years. This color additive was approved for drug and cosmetic use as a "coal tar" dye after enactment of the act in 1938 by a regulation published in the Federal Register of May 9, 1939 (4 FR 1922). Because D&C Red No. 19 was in use at the time the amendments were passed, FDA included it on the provisional list for use in drugs and cosmetics in the Federal Register of October 12, 1960 (25 FR 9759). The color additive is currently provisionally listed under § 81.1(b) for use in externally applied drugs and cosmetics, with a closing date of August 6, 1986. Specifications for certification of D&C Red No. 19 are currently listed under §82.1319 (21 CFR 82.1319).

The color additive D&C Red No. 19 is classified as an xanthene derivative. In 21 CFR Part 82, D&C Red. No. 19 is identified as principally the 3-ethochloride of 9-*o*-carboxyphenyl-6-diethylamino-3-ethylimino-3-isoxanthene (CAS Reg. No. 81-88-9).

B. Color Additive Petition

As noted in the Federal Register of August 6, 1973 (38 FR 21199), D&C Red No. 19 is the subject of a petition (CAP 9C0091) filed by the Toilet Goods Association, Inc. (now the Cosmetic, Toiletry and Fragrance Association, Inc. (CTFA), 1110 Vermont Ave. NW., Wash-

ington, DC 20005) for use in coloring drugs and cosmetics. The provisional listing for the color additive D&C Red No. 37, also a subject of the petition, was recently terminated by a regulation published in the Federal Register of June 6, 1986 (51 FR 20786). This action was taken by FDA because the petitioner, CTFA, had withdrawn that portion of its petition (CAP 9C0091) requesting the permanent listing of D&C Red No. 37. The petition was filed under section 706 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 376).

In the Federal Register of September 23, 1976 (41 FR 41863), FDA stated that the available toxicological studies were inadequate to support the permanent listing of several color additives, including D&C Red No. 19. The agency explained that the studies were deficient in the following respects:

1. Many of the studies were conducted using groups of animals, i.e., control and those fed the color additive, that are too small to permit conclusions to be drawn on the chronic toxicity or carcinogenic potential of the color. The small number of animals used does not, in and of itself, cause this result, but when considered together with the other deficiencies in this listing, does do so. By and large, the studies used 25 animals in each group; today FDA recommends using at least 50 animals per group.

2. In a number of the studies, the number of animals surviving to a meaningful age was inadequate to permit conclusions to be drawn today on the chronic toxicity or carcinogenic potential of the color additives tested.

3. In a number of the studies, an insufficient number of animals was reviewed histologically.

4. In a number of the studies, an insufficient number of tissues was examined in those animals selected for pathology.

5. In a number of the studies, lesions or tumors detected under gross examination were not examined microscopically.

The agency proposed that the continued provisional listing of several color additives, including D&C Red No. 19, be conditioned upon at least one petitioner undertaking new chronic feeding studies for the color additive. FDA intended that the required chronic studies would provide the necessary evidence upon which to determine whether to permanently list the color additives for use in drugs and cosmetics generally under section 706 of the act.

In the Federal Register of February 4, 1977 (42 FR 6992), it was announced that the petitioner agreed to sponsor the required chronic toxicity studies for the color additives. After D&C Red No. 19 had been provisionally listed for use in drugs and cosmetics for several years, in the Federal Register of March 27, 1981 (45 FR 18954), FDA extended the provisional listing until February 28, 1983, to provide time for completion of new chronic toxicity studies of D&C Red No. 19 and for review and evaluation of these studies.

In the Federal Register of February 4, 1983 (48 FR 5262), FDA terminated the provisional listing, and hence the approval, of the use of D&C Red No. 19 for coloring ingested drugs and cosmetics. FDA took this action because it concluded, on the basis of the animal experiments that had been performed as a condition of the provisional listing of this color additive, that D&C Red No. 19 is carcinogenic when administered in the diet of laboratory animals. In addition, the petitioner, the Cosmetic, Toiletry and Fragrance Association, Inc., withdrew the portion of its petition that pertains to the ingested use of this color additive. Therefore, D&C Red No. 19 could not be added to ingested drugs and cosmetics after February 4, 1983. The color additive has remained provisionally listed for use in externally applied drugs and cosmetics.

As discussed in the Federal Register of February 4, 1983 (FR 5262), the petitioner continued to seek permanent listing for the use of D&C Red No. 19 in external cosmetic and drug products that are not subject to incidental ingestion. On October 15, 1982, the petitioner submitted (1) analyses of the safety and legal issues raised by the external uses of the color additive and (2) data regarding skin penetration. The agency found these skin penetration data to be inadequate for determining the extent to which the color additive would be absorbed through the skin under conditions of use.

CTFA asked the agency to delay its final decision until CTFA could perform new skin penetration studies. CTFA said that it would submit the results of those studies to the agency by early February 1983. On February 15 and 18, 1983, CTFA submitted a technical report on a percutaneous absorption study (Ref. 1), a report regarding subsidiary color content in the sample of radiolabeled color additive used in the percutaneous absorption study (Ref. 2), a review and analysis of scientific studies, and an assessment of the risk from the use of D&C Red No. 19 in external cosmetic and drug products (Ref. 3). The agency agreed to review these data, along with the various arguments that CTFA presented in its February 15, 1983, submission, before reaching a conclusion on the safety of the use of D&C Red No. 19 in externally applied drugs and cosmetics. Because its review of the CTFA submissions and of the scientific and legal issues raised by this matter took longer than the agency anticipated, FDA had to extend the provisional listing of the color additive on a number of occasions. The agency established the current closing date of August 6, 1986 for the provisional listing of D&C Red No. 19 for use in externally applied drugs and cosmetics by a rule published in the Federal Register of June 6, 1986 (51 FR 20786). In that notice, the agency also announced its decision to permanently list the color additive for its external drug and cosmetic uses. This notice explains the bases for that

decision and the conclusion that the use of D&C Red No. 19 as a color additive in externally applied drugs and cosmetics is safe within the meaning of section 706 of the act.

C. Citizen Petition Filed by Public Citizen Health Research Group

On December 17, 1984, the Public Citizen Health Research Group (Public Citizen) petitioned FDA to ban the use of the color additives that remained provisionally listed. On January 22, 1985, Public Citizen filed a complaint in the District Court for the District of Columbia seeking the same relief. Public Citizen alleged that, by continuing to provisionally list the color additives, including D&C Red No. 19, FDA had violated the Color Additive Amendments to the act, as well as those provisions of the Administrative Procedure Act (5 U.S.C. 706 (1)) that pertain to unreasonable delay of agency action. Public Citizen sought to enjoin FDA from using the provisional list or any other means to allow the marketing of the provisionally listed color additives.

On June 21, 1985, the Commissioner of Food and Drugs sent to Public Citizen a detailed response to the petition. In his response, the Commissioner carefully reviewed and discussed the arguments and information submitted in support of the petition. The Commissioner concluded that the public health would not be endangered by the continued marketing of the color additives while scientific, legal, and policy issues were addressed and, therefore, the Commissioner denied the petition.

On February 13, 1986, Judge Stanley S. Harris granted FDA's motion for summary judgment and dismissed Public Citizen's complaint. *Public Citizen et al.* v. *DHHS, et al.*, No. 85-1573 (D.D.C. February 13, 1986). Public Citizen has appealed Judge Harris' decision.

III. Review of Provisionally Listed Color Additives by a Scientific Review Panel

In the proposal to extend the closing dates for the provisional listing of certain color additives, including D&C Red No. 19 (50 FR 26377; June 26, 1985), FDA announced that the Commissioner had established a scientific review panel (panel) of Public Health Service scientists to evaluate data and report on the risk assessment issues presented by the use of six color additives: D&C Red No. 8, D&C Red No. 9, D&C Red No. 19, D&C Red No. 37, D&C Orange No. 17, and FD&C Red No. 3.

FDA asked the panel to consider several scientific issues that had been raised by FDA scientists about whether a reliable assessment of the risk from the use of these additives could be conducted. Specifically, one issue was whether, for each additives, unidentified contaminants, rather than the principal color component, could be responsible for the observed carcinogenic effects in animal testing, and whether any such unknown impurities or components may be absorbed through the skin to a greater or lesser extent that other parts of the additive. The panel was charged with examining this impurities issue and, further, with addressing the issue of whether a risk assessment calculation could be made from the available data, and, if so, whether the risk assessments before the agency were properly calculated.

In the Federal Register of March 6, 1986 (51 FR 7856), FDA announced the availability of the final report of the panel. The report is entitled "Report of the Color Additive Scientific Review Panel, September 1985, Docket No. 86N-0039." A copy of the report is available to the public for review at the Dockets Management Branch (address above). Requests for copies of the report should be identified with Docket No. 86N-0039.

In the report, the panel concluded that the risk assessments submitted by the petitioners for several of the color

additives, including D&C Red No. 19, are consistent with current acceptable usages in risk assessment. The panel also concluded that legitimate issues with regard to impurities had been raised but could be addressed by making reasonable and appropriate assumptions about the possible influence that such impurities might have. The panel concluded that the range of lifetime risk presented by external exposure to D&C Red No. 19 was extremely low. The report of the panel was also submitted to peer review and subsequently published in *Risk Analysis*, 6:2:117-154, 1986, thereby broadly providing the risk analysis assessment to the scientific community. These findings will be discussed in greater detail below.

IV. Overview of the Final Rule

FDA has evaluated all the available evidence regarding the safety of D&C Red No. 19. Based upon this evaluation, FDA finds that the use of D&C Red No. 19 in externally applied drugs and cosmetics is safe. Although the external uses involve, based on conservative statistical analysis, a theoretical carcinogenic risk, the agency finds that this risk is so trivial as to be effectively no risk at all. For these reasons, the agency has decided to permanently list these uses of D&C Red No. 19.

The remainder of this document describes the information and advice relied upon by the agency in reaching its conclusion as to the safety of D&C Red No. 19 as a color additive for externally applied drugs and cosmetics. First, the agency evaluates the available data resulting from toxicology testing of D&C Red No. 19. In the next section, the agency discusses CTFA's safety evaluation of the same data. Next the agency deals with CTFA's arguments and questions concerning the relevance of the toxicology tests to the determination of the safety of the external drug and cosmetic uses of D&C Red No. 19. In the following section, FDA discusses CTFA's assessment of the extent of human exposure resulting from the external drug and cosmetic uses of D&C Red No. 19.

In the remaining sections, FDA discusses CTFA's low dose carcinogenic risk assessment approach, the report of the panel, and the panel's conclusions regarding the propriety of relying upon the available data to conduct risk assessments for use by a government regulatory agency. The next section addresses certain concerns raised by the panel concerning the safety of D&C Red No. 19 and the agency's resolution of those concerns. The section also discusses the agency's reliance on the *de minimis* doctrine to reach the conclusion that D&C Red No. 19 is safe for use in externally applied drugs and cosmetics and that the proscriptions of the Delaney Clause should not be invoked in this matter. The final section announces the permanent listing of D&C Red No. 19 subject to certification specifications and a restriction on the extent of its use.

V. Toxicology Testing of D&C Red No. 19

A. *Old Studies*

The agency previously reviewed during the petition evaluation reports of several toxicity studies of D&C Red No. 19 involving rats, dogs, mice, and rabbits. The studies included acute oral toxicity studies, acute intravenous toxicity studies, subacute feeding studies, dermal toxicity studies, chronic toxicity studies, metabolism studies, teratogenicity studies, and reproductive toxicity studies. These studies did not produce any evidence of adverse effects, indicating that the color additive would be safe for the petitioned use in externally applied drugs and cosmetics. Based on data from dermal toxicity studies, D&C Red No. 19 was also not found to be carcinogenic upon biweekly application to the skin of mice over their lifetimes.

B. New Long-Term Feeding Studies

The new studies represent current state-of-the-art toxicological testing. The protocols for these studies have

benefited from knowledge of deficiencies in previously conducted carcinogenesis bioassays and other chronic toxicity studies. The use of large numbers of animals of both sexes, pilot studies to determine maximum tolerated dosages, two control groups (thereby effectively doubling the number of controls), and in utero exposure in one of the two species tested (the rat) significantly increase the power of these tests for detecting dose-related effects. The studies were designed and conducted in full compliance with FDA's good laboratory practice regulations (21 CFR Part 58) and were subject to FDA inspection while they were being conducted.

In accordance with § 81.27(d) of FDA's regulations (21 CFR 81.27(d)), the petitioner, CTFA, submitted final reports of new chronic toxicity tests by February 28, 1982. FDA has reviewed the final reports of these studies, in which D&C Red No. 19 was administered in the diet to Charles River CD rats and Charles River CD-1 mice.

1. Mouse Study

In the CTFA-sponsored mouse study, the color additive was fed at levels of 0.005, 0.02, and 0.1 percent in the diet for 96 weeks to males and 108 weeks to females. A higher incidence of animals with hepatocellular neoplasms (carcinomas or adenomas) was observed in every female mouse dosage group than in the untreated control groups. The combined incidence of female mice with either hepatocellular adenomas or carcinomas was: high-dosage group—17/58 (17 animals with neoplasms out of 58 mice examined), mid-dosage group—7/60, low-dosage group—5/58, and control groups—4/114. The incidence of animals with hepatocellular neoplasms in the high-dosage group was significantly higher than that in the control groups using the Fisher's Exact Test ($p<0.0001$). The response observed was dose-related.

Furthermore, most of the hepatocellular neoplasms observed in the high- and mid-dosage groups of female mice

were malignant neoplasms. Historical data on control animals show that female mice have a low spontaneous incidence of malignant hepatocellular neoplasms. Although the treated male mice in this study also showed an increased incidence of hepatocellular neoplasms when compared with concurrent controls, the incidence in each treated male group was within the range of historical controls. Therefore, the agency concludes from these data that dietary exposure to D&C Red No. 19 causes an increase in the number of female mice with hepatocellular neoplasms.

2. Rat Studies

CTFA sponsored two long-term feeding studies in rats in which D&C Red No. 19 was administered in the diet following in utero exposure. The first study included two control groups and three treated groups with dose levels of 0.002, 0.005, and 0.02 percent of the diet. A second study had a single dose level of 0.075 percent of the diet and a separate control group. In the second study, the number of treated male rats (18/69) with either a malignant or benign follicular cell tumor of the thyroid gland was higher than that of the controls (2/70) using the prevalance test ($p<0.0001$). An earlier chronic study in rats had displayed no treatment-related increase in tumors, but enlargement of the thyroid glands was associated with treatment (Ref. 5).

The spontaneous occurrence of follicular cell tumors of the thyroid gland was uncommon in the control groups of the recent provisional list color additive feeding studies with the same design. The agency concludes that the increased incidence of male rats with follicular cell tumors is a treatment-related effect. On the basis of this evidence, the agency concludes that, when administered in the diet, D&C Red No. 19 induces neoplasms in the thyroid gland of male rats.

In addition, in the highest dosage group (0.075 percent of the diet), the incidence of male rats with parathyroid tumors (8/55) was higher (p=0.005) than that of the concurrent control group (0/56). The agency has determined that this evidence is a sufficient basis upon which to conclude that the dietary treatment with D&C Red No. 19 also caused a tumorigenic effect in the parathyroid of male rats.

C. *Agency Conclusion Regarding the Ingested Uses of D&C Red No. 19*

No significant data base has been developed concerning the toxicity of D&C Red No. 19 since the agency concluded in the Federal Register of February 4, 1983 (48 FR 5262) that the color additive is carcinogenic when administered in the diet of laboratory animals. The agency's conclusion was based on the observed increased incidence of female mice with hepatocellular neoplasms and a treatment-related increased incidence of male rats with thyroid follicular cell neoplasms and parathyroid adenomas (Ref. 6).

Based upon the petitioner's withdrawal of that part of its petition requesting permanent listing of D&C Red No. 19 for use in ingested drugs and cosmetics (48 FR 5262); and the agency's conclusion that the color additive is carcinogenic when administered in the diet, the agency terminated the provisional listing of D&C Red No. 19 for such use.

VI. CTFA's Safety Evaluation

In its submissions, CTFA presented several arguments that raise questions about the relevance of the ingestion studies to a determination of the safety of the external uses of D&C Red No. 19. In the following sections the agency reproduces CTFA's arguments, then evaluates them.

A. Differences in Reported Incidence Figures

In its submission of February 15, 1983, CTFA noted that the data on the mouse study and the second rat study reported by FDA in its order terminating the provisional listing of D&C Red No. 19 for use in ingested cosmetics and drugs differed from those reported by the testing laboratory. CTFA stated that it was not aware of the reason for the differences.

Based on FDA's preliminary review of data from the mouse and rat chronic feeding studies, FDA concluded that it was necessary to request all available microslides of liver sections from the mouse study and of thyroid/parathyroid slides from the two rat studies with D&C Red No. 19. The purpose of the FDA histopathology review was to verify the microscopic findings presented by CTFA. Data as reported by the testing laboratory and FDA pathologists are tabulated below. The incidence is reported as the number of animals with tumors per the total number of animals suitable for evaluation.

1. Mouse Study

INCIDENCE OF MICE WITH HEPATOCELLULAR NEOPLASMS FROM THE TESTING LABORATORY'S REPORT

Treatment of group	Males	Females
1 and 2 (0%)	17/119	4/115
3 (0.005%)	14/60	6/60
4 (0.02%)	12/59	8/60
5 (0.1%)	15/59	19/60

INCIDENCE OF MICE WITH HEPATOCELLULAR NEOPLASMS FROM FDA REPORT

Treatment group	Males	Females
1 and 2 (0%)	16/115	4/114
3 (0.005%)	12/58	5/58
4 (0.02%)	12/59	7/60
5 (0.1%)	15/56	17/58

FDA has combined the data on hepatocellular adenomas and carcinomas from tables in the CTFA submission into one table to make the data comparable to FDA's tabulations.

Because of differences in interpretation of the microscopic lesions by different pathologists (affecting numerator terms) and in choice of tissues suitable for histological diagnosis (affecting denominator terms), incidences reported by FDA differ slightly from those reported by the testing laboratory. The data in both presentations, however, show a dose-related increase in incidence of liver neoplasia in treated female mice and support the conclusion that dietary exposure to D&C Red No. 19 causes liver neoplasia in female mice.

2. Second Rat Study

INCIDENCE OF RATS WITH THYROID FOLLICULAR CELL TUMORS FROM THE TESTING LABORATORY'S REPORT

Treatment group	Sex	Adenomas	Carcinomas
Control (0%)	Males	2/57	1/57
	Females	2/57	0/57
Treated (0.075%)	Males	12/56	5/56
	Females	5/55	1/55

INCIDENCE OF RATS WITH THYROID FOLLICULAR CELL TUMORS FROM FDA REPORT

Treatment group	Sex	Adenomas	Carcinomas
Control (0%)	Males	1/70	1/70
	Females	2/68	0/68
Treated (0.075%)	Males	13/69	5/69
	Females	7/69	1/69

The differences in numbers of tumors (numerator terms) between the laboratory report and FDA's report are minor and are the result of interpretation by different pathologists. The denominator figures used in the FDA report reflect the total number of thyroid microslides submitted from each group, including the animals

sacrificed at the 1-year-interim period. The denominator figures in the testing laboratory report do not include the interim-sacrificed animals. A treatment-related increase in incidence of male rats with thyroid follicular cell tumors is shown in both presentations. Thus, the conclusion from both presentations is the same, namely, that dietary exposure to D&C Red No. 19 causes an increase in the number of male rats with thyroid follicular cell tumors.

B. Interpretation of Maximum Tolerated Dose

In the submission dated February 15, 1983, CTFA asserted that the 0.075 percent dose level of the second rat study exceeded the maximum tolerated dose (MTD) and thus violated the National Cancer Institute (NCI) guidelines for carcinogenicity testing (National Cancer Institute, *Guidelines for Carcinogen Bioassay in Small Rodents* (1976)). CTFA claimed that this dose level exceeded the MTD because it caused a substantial reduction in body weight gain in both males and females, and that the size of the dose was a reason for questioning the carcinogenic effect observed with this dose.

The NCI Guidelines define the MTD as "the highest dose of a test agent given during the chronic study that can be predicted not to alter the animals' normal longevity from effects other than carcinogenicity." The guidelines also state that the MTD "should be the highest dose that causes no more than a 10 percent weight decrement, as compared to the appropriate control groups; and does not produce mortality, clinical signs of toxicity, or pathogenic lesions (other than those that may be related to a neoplastic response) that would be predicted to shorten the animals' natural life span."

If the MTD is exceeded, there may be an insufficient number of test animals at risk and possible late-developing tumors would not be observed. Thus, the major concern about exceeding the MTD is that an erroneous

negative result may be obtained. In the present study the survival of female rats was lower than normal, which may explain the failure of females to demonstrate a significantly increased incidence of thyroid follicular cell tumors. Thus, although the NCI guidelines may have been "violated" in the case of the female rats, the effect of this would be to mask a possible carcinogenic response.

In any event, there is no indication whatsoever that the MTD was exceeded in the male rats tested. Although the treated male rats experienced a reduction in weight gain, of 8 to 9 percent, their survival was unaffected and they manifested increased numbers of tumors. Furthermore, in the male rats no clinical signs of toxicity or pathogenic lesions were noted other than those related to the neoplastic response. These facts establish that at least for the male rats, the MTD was not exceeded. Moreover, if it was exceeded for the female rats, the effect is the loss of possible confirmatory information regarding the carcinogenicity of the compound. CTFA's arguments on this issue are of little relevance and impact.

C. Significance of Mouse Liver Tumors

In the submission dated February 15, 1983, CTFA questioned the significance of the mouse liver tumors observed in the chronic tests by contending that "* * * the natural incidence of liver cancer is relatively high in inbred mice as compared to humans and other species, possibly indicating the presence of a latent population of initiated tumor cells in these mice. Substances that induce chronic liver toxicity and cell degeneration and regeneration might thus be capable of promoting this latent population of neoplastic cells to overt neoplasm in mice." CTFA stated further that "* * * there is no agreement within the scientific community on extrapolating carcinogenesis risk to humans on the basis of evidence of liver tumors in mice," and that "some respected investigators consider the liver of the inbred mouse to be an invalid system for carcinogenicity testing."

FDA is aware that the relevance of the production of hepatocellular tumors in mice in predicting cancer risk in humans has been debated extensively over the past several years. The debate on the relevance of mouse hepatocellular tumors does not obviate the necessity for a careful evaluation of a study in which the finding occurs and of the relationship of that finding to the results in other studies with the test substance.

The liver, because of its location and important role in metabolism, is a frequent target organ for toxic effects of compounds administered by the oral route. Substances absorbed from the gastrointestinal tract reach the liver in amounts much higher than the amounts to which other organs are generally exposed. Metabolic conversion of a substance to a more toxic metabolite often occurs in the liver, and the liver cells are exposed to the highest concentration of the active agent. Thus, hepatotoxic effects may be the only toxic effects observed. For this reason the agency disagrees with CTFA's contention and believes that the liver tumors must be carefully considered.

CTFA's argument about the high incidence of liver cancer in inbred mice does not apply to the CD-1 mouse, the strain used in the mouse study. The background or control incidence of hepatocellular tumors in this strain is low compared to most mouse strains. Moreover, data submitted by CTFA on April 8, 1981, showed the following incidence of tumors in 16 control groups (more than 900 mice of each sex):

	Males	Females
Hepatocellular carcinoma	9.65±4.25%	0.63±1.03%
Hepatocellular adenoma	5.12±3.92%	1.17±1.21%

Thus, the incidence of hepatocellular tumors (carcinoma and adenoma) among female mice in the control groups was about 2 percent. In contrast, the incidence of hepatocellular tumors among female mice in the high-dose group was almost 30 percent.

The International Expert Advisory Committee to the Nutrition Foundation (the committee) described the following factors as important in determining whether the production of mouse hepatocellular tumors is the result of treatment and, therefore, relevant to an assessment of carcinogenic risk: (1) Incidence of tumors in treated animals is clearly higher than in concurrent controls; (2) incidence is also higher than in historical controls or dose related; (3) there is a decrease in time of onset in the treated animals; (4) there is a preponderance of malignant lesions in treated animals compared with the controls; and (5) tumors are observed at other sites in the mouse, or tumors are observed in other species. ("The Relevance of Mouse Liver Hepatoma to Human Carcinogenic Risk," September 1983.) Each of these factors is established in the case of D&C Red No. 19.

In the mouse study the incidence of female mice with hepatocellular tumors was, in fact, increased in comparison to the concurrent controls at both the mid- and high-dose levels, and the increase was dose related. The incidence of females with both hepatocellular carcinomas and hepatocellular adenomas in all the test groups also exceeded the range in historical controls. The combined incidence of high-dose female mice with hepatocellular neoplasms was more than 10 times the average combined incidence of historical controls with such tumors.

FDA recognizes that, with the small number of female mice with hepatocellular tumors in the control group, it is difficult to compare the time of onset of tumors in the control group with those in the treated group. However, all of the hepatocellular tumors found in the control female mice were found in animals sacrificed at completion of the study or dying within a month of completion. In contrast, hepatocellular carcinomas were found in several treated female mice dying well before completion of the study. The observation of tumors at an earlier time (particularly malignant tumors) is suggestive of a treatment

effect leading to earlier onset of tumors. The hepatocellular tumors in the high-dose female group were predominantly carcinomas (malignant tumors) whereas the hepatocellular tumors in the control females were all adenomas (benign tumors).

Further, an increase in the incidence of male rats with thyroid follicular tumors (carcinomas and adenomas) and parathyroid adenomas was observed in the high-dose chronic study of D&C Red No. 19.

Thus, based on its analysis of the data using the factors outlined by the committee, FDA has concluded that the hepatocellular tumors observed in the female mice were the result of the ingestion of D&C Red No. 19 and must be considered in any evaluation of the safety of the color additive.

D. Mechanism of Carcinogenicity

CTFA stated in its submission of February 15, 1983, that it had reviewed the information available on D&C Red No. 19 to determine the likely mechanism of action of the additive. CTFA acknowledged that the precise mechanism of action could be determined only through extensive further testing but contended that the information that is currently available does not demonstrate that D&C Red No. 19 is a primary (or initiating or direct-acting or genotoxic) carcinogen.

In support of its contention, CTFA relied upon the results of four studies on the mutagenicity in *Salmonella typhimurium* (Ames test) of material identified as either D&C Red No. 19 or Rhodamine B (a common name for the color additive). In two of the studies, negative results were observed (Muzzall and Cook, *Mutation Research*, 67:1 (1979); and Green and Pasteuka, *Journal of the National Cancer Institute*, 64:665 (1980)). In the other two studies, positive results were observed in the presence of a rat-liver metabolic system (Brown et al., *Mutation Research*, 66:181 (1979); Nestmann et al.,

Cancer Research, 39:4412 (1979)). CTFA concluded that impurities could be responsible for most of the mutagenic activity observed in the latter studies. On the basis of this conclusion, CTFA asserted that D&C Red No. 19 is either not mutagenic or is a very weak mutagen, and that therefore the results are inconsistent with the color additive being a strong primary carcinogen.

CTFA's suggestion that impurities in D&C Red No. 19 were the agents responsible for this additive's mutagenic and carcinogenic activity does not provide any assurance that the color additive does not pose a cancer risk. For example, even if the impurities are carcinogenic, the color additive itself could also be carcinogenic. In fact, the color additive as a whole, as discussed above, has been tested and found to induce cancer. Thus, FDA concludes that the arguments CTFA presented regarding mutagenicity do not provide evidence that D&C Red No. 19 is not a carcinogen.

CTFA also argued that it is possible that a secondary mechanism may have caused each of the types of tumors observed in the chronic bioassays of D&C Red No. 19. As discussed above, CTFA stated that liver cancer is relatively high in inbred mice as compared to humans and other species, possibly indicating the presence of a latent population of initiated tumor cells in these mice. CTFA also suggested that a thyroid hormone imbalance and subsequent chronic hyperplastic stimulation is possibly the mechanism for the induction of thyroid tumors in the rat. Finally, CTFA stated in its submission of February 15, 1983, that risk assessment shows that "the best-fitting version of the multistage model for the rat thyroid data contained no linear terms, only higher-order terms." CTFA stated that this type of curve is compatible with a dose-response relationship that has a threshold, and thus that this result may mean that the color additive is a secondary carcinogen.

The arguments presented by CTFA are speculative and CTFA has not submitted factual scientific evidence to support the hypothesis that D&C Red No. 19 does indeed act as a secondary carcinogen. In fact, in one of its submissions, CTFA has acknowledged that "* * * there is inadequate evidence at this time to demonstrate a secondary mechanism of action that would justify use of a safety factor approach." (See Ref. 3, NOEL Safety Factor Approach, p. 39, CTFA submission, February 15, 1983.) For all these reasons, FDA concludes that CTFA has failed to present any basis on which to find that D&C Red No. 19 is a secondary carcinogen.

E. Percutaneous Absorption Studies and Assessing the Risk From External Exposure

FDA finds that there is no reason, based on CTFA's arguments presented above, to change its conclusion, as stated in the Federal Register of February 4, 1983 (48 FR 5262), that D&C Red No. 19 is carcinogenic upon ingestion. Having made such a finding, the agency must consider the relevance of the ingestion studies to the noningested uses of the color additive (see section 706 (b) (5) (B) (ii) of the act). D&C Red No. 19 induces cancer at sites remote from the alimentary tract, indicating that it is systemically absorbed before acting as a carcinogen. FDA has consistently held that ingestion studies are appropriate for evaluating the safety of the externally applied uses of such a color additive if the additive is shown to penetrate the skin. See Ref. 7, e.g., 43 FR 1101, 1103; January 6, 1978. A color additive that penetrates the skin can be distributed to remote sites in a manner analogous to the distribution that occurs when an ingested color additive enters the circulatory system from the gastrointestinal tract. Therefore, in its consideration of the safety of D&C Red No. 19, the agency evaluated the results of the percutaneous absorption studies with D&C Red No. 19.

An in vitro percutaneous absorption test is designed to measure the ability of a particular substance, such as a color additive, to penetrate excised skin under conditions simulating human use. Information on skin penetration is important in determining the exposure to a color additive used in topical applications.

FDA evaluated the first percutaneous absorption study submitted by CTFA and informed CTFA in a conference held on November 23, 1982, of the deficiencies in the study that prevented the agency from determining whether the color additives would penetrate human skin under normal conditions of use. FDA could not determine whether D&C Red No. 19 would penetrate the skin from the test data because the dosage levels of the applied color additive, the treatment of the excised skin, and the solvent systems used did not appropriately reflect the expected conditions of use of the color additive. Therefore, because of the deficiencies in the absorption study, FDA advised CTFA that the data were not sufficient to support the safety of the externally applied uses of the color additives.

CTFA notified FDA in a letter of December 9, 1982, that it intended to conduct an additional in vitro percutaneous absorption study with D&C Red No. 19 and requested that FDA review the study design. FDA reviewed the initial protocol for the study and, after the agency commented on that protocol, a subsequent protocol that CTFA had revised according to the agency's suggestions. FDA advised CTFA by letter of January 18, 1983, that it concurred with the revised protocol proposed for testing the skin permeability of D&C Red No. 19 and D&C Red No. 19 Aluminum Benzoate Lake. FDA informed the petitioner that if it submitted the data promptly, the agency would consider such data along with the other scientific and legal matters involved in the agency's decision on the listing of the color additive for external use. FDA also advised CTFA that the agency

could not guarantee that percutaneous absorption studies could resolve all the scientific and legal issues involved in listing the color additive for external use. The final report of the absorption study was received by FDA on February 18, 1983.

FDA finds that the study was performed, in general, in a satisfactory manner. The test data clearly show that radiolabeled material from D&C Red No. 19 passes through the skin in small, but measurable amounts. Therefore, the agency concludes that some systemic exposure to the color additive may occur from the use of externally applied drugs and cosmetics containing D&C Red No. 19, and that the ingestion studies that show this color additive to be a carcinogen are appropriate for evaluating the safety of the externally applied uses of D&C Red No. 19 (Ref. 7).

CTFA has argued, however, that it is possible, using the data from the biossays and the skin penetration studies, to assess the carcinogenic risks from the external use of the color additive and to use the results of that assessment in deciding on the safety of the external uses of the additive. CTFA has also argued that such an assessment demonstrates that D&C Red No. 19 is safe when used in externally applied products.

The carcinogenic risk from the use of an externally applied carcinogenic color additive is determined by (1) the amount of color additive applied to the skin and the frequency of application, (2) the concentration of carcinogenic agents in the color additive, (3) the potency of the carcinogenic agents, and (4) the fraction of the applied carcinogenic agents that penetrate the skin.

The risk estimates submitted by CTFA are based on the assumptions (1) that the principal color component is the carcinogenic agent, (2) that the radiolabeled material penetrating skin is representative of the whole

color additive, and (3) that 100 percent of the carcinogenic agent is absorbed from the alimentary tract into the blood stream in the animal feeding studies.

FDA's scientists questioned CTFA's assumptions because an argument could be made that a contaminant is responsible for the carcinogenic response. Color additives are not pure substances and normally contain intermediates, subsidiary colors, and other contaminants from intermediates and from side reactions. Although the carcinogenicity of D&C Red No. 19 was revealed by an animal bioassay, the bioassay did not establish whether the carcinogenic response was produced by the principal color component or by one or more of its contaminants. It is theoretically possible that one of the contaminants could be responsible for the production of the carcinogenic response.

CTFA's assumption that the radiolabeled material was representative of the whole color additives (and that, therefore, there is no need to be further concerned with possible impurities) could not be substantiated. CTFA measured only the radioactivity of the substance that penetrated the skin and could not identify the components that actually penetrated the skin.

Moreover, FDA's scientists could not determine from the data submitted by CTFA which constituents of the color additive penetrated skin, or whether impurities in the color additive would penetrate skin in the same manner as the primary color that was tested. It is possible (1) that the actual carcinogen could be a contaminant that penetrated the skin but was unlabeled and therefore undetected; (2) that virtually none of the principal color component penetrated the skin, and that the radioactive material found could be due to carcinogenic contaminants; and (3) that the degree of skin penetration by the actual carcinogenic agent is greater than that estimated by CTFA based on its assumption that the prin-

cipal color component of D&C Red No. 19 is the carcinogen.

Another assumption by CTFA, that 100 percent of the carcinogenic agent is absorbed from the gastrointestinal tract, was questioned by FDA's scientists because few chemicals are ever completely absorbed. There are many reasons for poor or limited absorption of chemical substances from the gastrointestinal tract, including (1) the instability of the chemical in acidic fluids, (2) enzymatic breakdown by digestive juices, (3) destruction by intestinal microorganisms, and (4) lack of liquid solubility (Ref. 8).

FDA asked the panel to review CTFA's assumptions and the agency's concerns about exposure to impurities in D&C Red No. 19. The panel revised several of CTFA's assumptions and concluded that the agency's concerns regarding impurities, although important, can be addressed by making reasonable and appropriate assumptions about the possible effects impurities might have. The panel found it highly unlikely that impurities would significantly influence the risk assessment. The results of the panel's review are discussed in greater detail in a later section of this notice.

VII. CTFA's Assessment of Exposure to D&C Red No. 19

In the report submitted on FDA on February 15, 1983, CTFA outlined the approach to estimate human exposure to D&C Red No. 19. CTFA estimated the cumulative amount of D&C Red No. 19 absorbed by an individual based upon the products in which the color additive was used, the amount of each product used per application, the frequency of use of each product, the concentration of the color additive in each product, and the level of dermal absorption.

CTFA reported that by using both a prospective and a retrospective approach, it had determined the exposure

to D&C Red No. 19 through external cosmetic and drug product use. Data on the frequency of use of various external cosmetic and drug products came from two sources. The first is a 1-week prospective survey of female participants. The participants recorded the number of times in a week they used a range of cosmetic products including face powders and rouges, hair cosmetics, nail products, bathwater products, wash-off products, and various other externally applied cosmetic products. For products used less often than once per week, they were asked to report how often they generally used such products. The second source of data on frequency of use is from a retrospective survey of 1,129 customers of a chain of stores run by a major cosmetic manufacturer. Because the individuals in this survey were customers of specialty cosmetics stores, they are likely to have above-average usage patterns. For both sets of data, for each product, CTFA listed an average and an upper 90th percentile value of frequency of usage.

Data on the amount of each product per application were provided from the responses to a survey of CTFA member companies to obtain the results of existing studies on this subject. The values are the averages for each product as reported in CTFA's survey.

The February 15, 1983, report presented data derived from the skin absorption study conducted by Dr. Thomas J. Franz on the proportion of the D&C Red No. 19 contained in each product that is likely to be absorbed. The skin absorption study conducted by Dr. Franz is described in detail in a separate report (Ref. 1). Briefly, the absorption of ^{14}C-labeled color additive through half-thickness human abdominal skin was studied using Franz diffusion cells. Absorption under each of 11 experimental conditions described in the study was tested on duplicate sections of skin from each of 3 donors. The receptor phase (isotonic saline, pH 7.6, 37° C.) was sampled for radioactivity and replaced by fresh saline at 4, 8, and 12

hours, and at 12-hour intervals until four steady-state readings were obtained, or 72 hours after application of the color additive. In some exposures, sample collection continued at 12- or 24-hour intervals up to 120 hours. The hourly and daily absorption rates and the percentage of the applied color additive absorbed over 3 days were calculated.

CTFA believes that the amount of D&C Red No. 19 applied per square centimeter in these experiments was similar to or greater than the corresponding amount that would be applied in externally applied cosmetics and drugs. Hence, it concluded that the experimental permeability data are likely to be reasonably applicable to absorption of the color additive from a cosmetic or drug applied to the skin.

CTFA provided estimates of the amount of color additive absorbed daily by combining the information on daily usage (upper 90th percentile) of the external cosmetic and drug products with data on the D&C Red No. 19 content of the products (average and maximum) and estimates of the proportion of the color additive absorbed. CTFA emphasized that these data were deliberately chosen to overestimate exposure.

The usage values are upper 90th percentile values. The concentration of D&C Red No. 19 is presented both as the maximum used in any formulation of each product type and as the average concentration in formulations that contain D&C Red No. 19. For all product categories, there are many formulations that do not contain D&C Red No. 19 and these formulations are not included in calculating the "average" values listed. Thus, a true "average" would be much lower, and the "average" values listed greatly overestimate the extent of exposure to D&C Red No. 19 from its use in externally applied cosmetic and drug products.

By summing the values of D&C Red No. 19 absorbed per day for each product containing the color additive,

CTFA determined the "worst case" maximum amount absorbed for all or any combination of products. Summing all values gives a daily "worst case" absorption of 3.27 to 3.77 micrograms or 0.0062 to 0.071 microgram per kilogram per day for a 53 kilogram adult female using all products containing the maximum level of D&C Red No. 10 at the upper 90th percentile usage frequency.

The panel, at FDA's request, critically evaluated CTFA's assessments and underlying assumptions. A discussion of the panel's evaluation is provided in a later section of this notice.

VIII. CTFA's Low-Dose Carcinogenic Risk Assessment Approach

CTFA calculated both the "best conservative estimate" and the "upper bound estimates" of risk from the use of D&C Red No. 19 in externally applied cosmetics and drugs, using currently accepted methods of risk assessment. The low-dose risk assessment proceeds in four steps:

1. Selection of the set of data on tumor incidence judged most appropriate as the basis for inference of human risk;

2. Extrapolation of these data to provide "best estimate" calculations, thus providing a range of risk to mice and rats at low-dose levels;

3. Extrapolation of the potential risk to humans at low-dose levels; and

4. Calculation of the potential risk to humans at the likely level of exposure from known patterns of use.

CTFA acknowledged that each of these steps required the use of assumptions with varying degrees of certainty. It was standard procedure by CTFA to make highly conservative "worst case" assumptions at each step, so that the final estimates likely overstated the actual risks by large factors. In its report, CTFA presented both "best

conservative estimate" and "upper bound estimate" calculations to illustrate the range of potential risk. The "best conservative estimate" was based upon the extrapolation curve that best fits the experimental data, but also included such highly conservative "worst case" elements as the assumption that an individual consumer will be in the upper 90th percentile for frequency of use of all cosmetic products and will use only those cosmetic products that contain D&C Red No. 19 at the maximum concentration. The "upper bound estimate" includes all "worst case" assumptions.

The CTFA risk assessment combined adenomas and carcinomas from the mouse liver tumor data and used the "worst case" maximum projections of human exposure and skin penetration. The multistage extrapolation model using the "worst case" maximum human exposure provides a "best conservative estimate" of potential lifetime risk to humans of $1x10^{-7}$ (1 in 10 million), and an "upper bound estimate" of $1.5x10^{-7}$ (1 in 6.7 million).

For the rat thyroid tumors, CTFA again combined both adenomas and carcinomas in order to provide a very conservative "worst case" estimate of potential risk to humans. The multistage extrapolation model using the "worst case" maximum human exposure provided a "best conservative estimate" of potential lifetime risk to humans of $2.3x10^{-14}$ (1 in 43 trillion) and an "upper bound estimate" of $3.1x10^{-7}$ (1 in 3.2 million).

IX. Review of D&C Red No. 19 by the Scientific Review Panel

FDA's evaluation of the petitions for permanent listing of these color additives, and other available information, raised questions concerning whether CTFA's risk assessment was valid. As discussed above, FDA convened the panel to address these questions. The membership of the panel is outlined in the Federal Register of June 26, 1985 (50 FR 26379), which is incorporated by reference.

The panel was charged to evaluate the available data, information, and views on the color additives and to provide answers to the following questions:

1. Can valid quantitative risk assessments be performed for these color additives?

2. Does the available information support the data analysis and risk assessments that have been performed and are before the agency?

X. Report of the Color Additive Scientific Review Panel

The panel evaluated the possibility of performing a scientifically valid carcinogenic risk assessment on D&C Red No. 19 for externally applied drug and cosmetic uses. The panel did not consider risk assessments for other toxic endpoints—indeed, it was not necessary to do so because no safety concerns other than carcinogenicity have been associated with the external uses of D&C Red No. 19. The panel's report contains a discussion on the assumptions that must be made in conducting a risk assessment and the uncertainties that are associated with such assumptions. The report is supported by several recent government agency efforts directed at developing a consensus of risk assessment:

(1) The National Academy of Sciences Report on Risk Assessment;

(2) The Office of Science and Technology Policy Document on Chemical Carcinogenesis and

(3) The Executive Committee, Coordinating Committee on Environmental and Related Programs Report on Risk Assessment.

The report contains a scientific introduction section for the major topics being discussed as well as a section on the general assumptions used in risk assessment of colors. The report discusses the risk assessment for each of the color additives by discussing major topics for each and

the color additive-specific assumptions used, with the focus on the risk under practical conditions of use. Each chapter also contains a risk characterization section which discusses the risk assessment of the individual color additive.

In its report, the panel critically reviewed the risk assessments submitted by CTFA. This included a detailed examination of the risk assessment methodology used by CTFA. In a summary chapter of the report (Chapter 9) the Panel stated that:

> In order to obtain a better perspective on the very complex and multifaceted problem of assessing exposure and toxic effect of the dyes, it was imperative to search for the many obvious or hidden, explicitly stated or implied assumptions associated with risk assessment of the dyes. In dissecting the presented problem into the smallest possible components, for which separate solutions might be formed, the Panel opted for starting with formulating the assumptions according to CTFA's line of reasoning (it should be emphasized, however, that CTFA made these assumptions to, presumably, derive a conservative risk estimate, while not necessarily supporting them). This was followed by a careful analysis of the validity of the statements, the possible alternatives to dealing with the gaps in knowledge and lack of information, and the quantitative assessment of the impact of the assumption on the magnitude of the risk of cancer, assuming that the dyes do pose such a risk to humans.
>
> While evaluating the many kinds of uncertainties in hazard identification, exposure assessment, and dose-response assessment, the Panel developed the view that, rather than limiting its role to analyzing CTFA's lines of reasoning, it attempt to use its analysis to generate modified risk estimates. This in-

cludes an estimate of the absorbed dose based on more "reasonable" assumptions than those used in the CTFA assessments.

In the risk characterization section in the various dye chapters in the report, the panel compared the 90th percentile and the average usage (based on reasonable estimates). For the purpose of presenting the panel's assessment of the numerous assumptions used in the CTFA risk assessments, the agency has summarized that portion of the panel's report which discusses the assumptions and the associated uncertainties. The summary below deals with assumptions which are relevant to all color additives reviewed by the panel.

A. The Panel's Assumptions Used in Hazard Identification

The panel generally accepted the assumptions used in the CTFA risk assessments largely because there seem to be no alternatives with higher degree of validity for the uncertainties involved and because they are consistent with what the panel understood FDA's policy to be. The panel believed the assumptions it relied upon to be conservative, i.e., are more likely to overestimate rather than underestimate the true risk.

The panel's assumptions concerning hazard identification were:

1. Because all six dyes of concern are animal carcinogens in some assay, they are suspect human carcinogens. (The panel made no evaluation of the weight-of-evidence for human carcinogenicity from the test animals.)

2. Orally administered or ingested dyes are equally well absorbed in animals and humans, regardless of the test concentration of the dye and of the vehicle used.

3. Studies involving high doses of a compound under test are appropriate for low-dose extrapolation.

B. The Panel's Assumptions Used in Exposure Assessment

The panel's general assumptions regarding exposure assessments were:

1. The dyes are equally absorbed in rodents and man.

2. Dyes which penetrate the skin are as effective in evoking a carcinogenic response as if ingested.

3. For each dye, exposure is for 60 years (in contrast to CTFA's use of 70 years) and risk is not influenced by age at exposure. The results in a correction factor of 6/7.

4. An arbitrary value should be used to reflect the fact that cosmetic products contain other dyes than those of concern (or no dyes at all). Compared to the CTFA estimate, this results in a correction factor of 0.5.

5. Based on data for D&C Red No. 19 only, the average concentration of all dyes in commercial products is 25 percent of the highest concentration allowed. Compared to the CTFA estimate, this results in a correction factor of 0.25.

6. The skin model used for the skin absorption studies is appropriate for assessing the exposure to absorbed dye. Although the model is likely to overestimate the risk, for products applied to the facial skin (skin penetration rates are likely to vary for different areas of the body), the model may underestimate the real absorption rate by a factor of 3.

7. In interpreting the results of the in vitro study on the absorption rates over time, the true absorption rate equals the steady state rate. Where the test did not reveal a steady state, twice the maximum rate at the end of 3 days approximates the true absorption rate.

8. Both types of CTFA surveys of the frequency of the use of dye containing products overestimate the frequency among the general population.

9. The absorbed amount of dye per day can be estimated by multiplying the amount of dye per day available for absorption by an absorption rate constant, as estimated from the in vitro tests. There is sufficient information however, to calculate a better, less conservative estimate.

10. For each dye, the total exposure is the sum of exposures to all products containing the same dye.

11. The amount of dye-containing product per application is approximately 5 to 10 milligrams per square centimeter.

12. With the exception of nail products, the composition of the vehicle used in the commercial products does not affect the absorption rate assessed with the in vitro skin model. There is insufficient information to generate a best estimate of the absorption rate for each kind of commercial vehicle.

13. In an appropriate vehicle, there is no difference in absorption rate between a primary dye and its lake.

14. Based upon consideration of the structure and toxicity of actual impurities found in certified lots, the skin penetrance rates of subsidiary colors are not likely to be significantly different from that of the principal constituent. The skin penetrance rates of the other substances of concern (e.g., residual starting materials) have, at most, an effect of multiplying the risk by 1.2. This results in a correction of CTFA's estimate of the exposure by a factor of 1.2.

The panel's product-specific assumptions regarding exposure assessments were:

1. The absorption rate for hair cosmetics is 1.2 percent of the applied amount. This results in a correction of CTFA's estimate by a factor of 0.6.

2. No absorption occurs from dyes in nail products (CTFA assumed that 1 percent of the applied amount will penetrate the skin).

3. For bathwater products, 2 percent of the applied amount reaches the skin.

4. For wash-off products (including bathwater products), there is an absorption of 25 percent (CTFA assumed an absorption of 50 percent and excluded bathwater products from this consideration). This results in a correction of CTFA's estimate by a factor of 2.

5. For products other than wash-off products, there is an absorption of 50 percent (CTFA assumed an absorption of 100 percent). This results in a correction of CTFA's estimate by a factor of 2.

C. The Panel's Assumptions Used in Dose-Response Assessment

1. In test animals, 50 percent of orally administered dyes are absorbed from oral studies and the carcinogenic response is caused by this absorbed portion. This results in a correction of CTFA's estimate by a factor of 2.

2. On a milligram per kilogram body weight basis, dose levels used in animal tests have the same quantitative effect on the cancer incidence in humans. There is insufficient information for assessing the best estimate of the correct dose unit for use in extrapolating animal risk to human risk of cancer.

3. The average body weight for an adult woman is 53 kilograms.

4. The linearized multistage model reflects the true relationship between dose and response. The linearized multistage model may offer no added protection, however, in the convex portion of the dose-response curve.

Low-dose linearity may overestimate the risk by several orders of magnitude if low-dose linearity is not present.

5. The most sensitive animal tumor data should be used to extrapolate risk from animal data to humans.

D. The Impact of the Panel's Assumptions on CTFA's Risk Estimate

In the chapters of the report concerning specific dyes, the panel applied the foregoing product- and dye-specific assumptions and correction factors to the usage data contained in the CTFA risk assessments. The panel also applied these assumptions to the survey estimates of 90th percentile exposure (the Risk/90 values) and average and "reasonable" estimates of exposure (Risk/Rea), thereby deriving revised risk estimates.

The impact on CTFA's risk assessment of the panel's general, quantifiable assumptions concerning exposure and dose-response are:

1. For skin absorption, a correction factor of 0.8 times the CTFA estimate (6/7x0.5x0.25x3x1.2x2).

2. For incidental ingestion of lip products, a correction factor of 6/7 times the CTFA estimate (a number of factors relevant only to skin absorption or not relevant to lipstick products do not apply).

3. At low dose levels, the risk of cancer, as computed with the linearized multistage risk model, is directly proportional to the dose levels.

The panel concluded that the correction factor of 0.8 for skin absorption is inconsequential when compared to the uncertainties in the assumptions that are difficult to quantify. The panel cautioned that the correction factor for skin absorption does not mean that the risk estimate is precise within 20 percent of the actual human risk. On the contrary, the figure merely represents the fact that, for the various quantifiable assumptions, un-

derestimations and overestimations of risk in the CTFA estimates basically cancel out.

The panel also noted that many of the assumptions are not quantifiable. The panel, following prudent public health policy, stated that it accepted assumptions which are likely to overestimate rather than underestimate risk in the cases difficult to quantify and is of the opinion that the human risk in the risk estimates it made is more likely to be over- rather than underestimated.

E. Specific Assumptions

The panel in its review of risk assessment for D&C Red No. 19 evaluated a number of CTFA's specific assumptions relevant to the color. The assumptions and the panel's revisions are as follows:

1. The absorption rate of dyes in emulsions equals 0.25 percent per day of the amount applied to the skin. CTFT assumed a 1 percent absorption rate.

2. For products based on mineral oil, the dye absorption rate equals less than 0.25 percent per day of the applied amount, as compared to CTFA's 0.5 percent. With regard to products based on castor oil, the absorption rate equals 0.04 percent (CTFA assumed 0.5 percent).

3. For aqueous products, except for those that need adjustment, the absorption rate per day equals 1 percent.

4. For talc products, 0.002 percent per day is absorbed from the amount applied.

The panel also utilized the following product-specific assumptions in risk characterization:

1. For hair cosmetics, CTFA assumed that 2 percent of the applied amount of dye reaches the skin. This is an overestimation requiring a correction factor of 0.6.

2. For nail products, the absorption of dyes is zero. CTFA assumed that 1 percent of the dye applied is available for absorption.

3. For bathwater products, 2 percent of the applied dye reaches the skin, where it is available for absorption.

4. For "wash-off" products, regardless how short the exposure time, the absorption rate is 25 percent of that of products used continuously. CTFA assumed a 50 percent rate.

5. For products other than "wash-off" products, not more than 50 percent of the amount applied is available for absorption. CTFA assumed that 100 percent of the applied amount is available.

F. The Panel's Interpretation of the Long-Term Studies

Before revising CTFA's risk assessments, the panel evaluated the available long-term studies of D&C Red No. 19 in laboratory animals. The panel agreed with FDA that the 0.075 percent dosage level of D&C Red No. 19 feeding study in rats showed that ingestion of the color additive resulted in an increased incidence of thyroid follicular tumors (adenoma and carcinoma) in treated males as compared with controls. The panel also agreed that the study appeared to be adequate and well-controlled, but noted that there was a lack of definitive information on the purity of the dye and the presence of impurities. Supplemental information indicated that levels of organic impurities were between 2 to 4 percent. The panel also agreed with FDA's conclusions regarding the CTFA-sponsored mouse study. The panel concluded that the study showed that feeding D&C Red No. 19 resulted in liver tumors in female mice.

G. Revised Risk Estimates

The panel's final step in evaluating the adequacy of CTFA's risk assessments on the external uses of D&C

Red No. 19 was to determine the total amount of dye absorbed per day. The panel applied the product and dye specific assumptions discussed above to the usage data results and calculated the total absorbed amount of dye to be:

0.42 microgram per day as an average of the prospective usage survey and 1.62 micrograms per day as the upper 90th percentile of the prospective survey (CTFA assumed 0.85 microgram per day and 3.27 micrograms per day, respectively), and

0.53 microgram per day as an average of the retrospective usage survey and 1.87 micrograms per day as the upper 90th percentile of the retrospective survey (CTFA assumed 1.06 micrograms per day and 3.77 micrograms per day, respectively).

The panel believed that the prospective survey is likely to be less biased than the retrospective study. The doses pertaining to the prospective study were, therefore, used for calculating adjusted risk estimates. At the low-dose levels resulting from use of cosmetics, using the linearized multistage extrapolation model, the dose-response curve is linear, meaning that the risk of cancer is directly proportional to the dose.

The following estimates are based on 53 kilograms as a lifetime weight average for women, and include the correction factor of 0.8 to adjust for the panel's view on the quantifiable general assumptions:

	Risk (CTFA/90)	Risk (CTFA/Avg)	Risk/90	Risk/Rea
Absorbed dose	3.27	0.85	1.62	0.42
Rat	2.7×10^{-7}	7.1×10^{-8}	1.1×10^{-7}	2.8×10^{-8}
Mouse	1.3×10^{-7}	3.4×10^{-8}	0.5×10^{-7}	1.3×10^{-8}

Risk (CTFA/90) is the CTFA risk estimate at the upper 90th percentile of exposure.

Risk (CTFA/Avg) is the CTFA risk estimate at "average" estimates of exposure.

Risk/90 is the risk estimate based on the panel's calculation at the 90th percentile of exposure.

Risk (REA) is the risk estimate based on the panel's calculation of a more reasonable estimate of exposure.

Absorbed dose is the estimated dose absorbed from external uses in micograms per day (panel estimate of the absorbed dose based on more "reasonable" assumptions than those used in the CTFA assessments).

Rat indicates that the data were derived from a rat study.

Mouse indicates that the data were derived from a mouse study.

These risk estimates are based on the reasonable estimates of exposure, whenever the panel believed that it was possible to make such an estimate. In situations where available data would allow for a choice between "degrees of reasonable estimate," the panel consistently selected the estimate associated with the higher risk.

If the dose conversion (metameter) from rodents to humans is made on a surface area basis rather than on a body weight basis (milligrams per square meter-day rather than milligrams per kilogram-day) the risk estimates would be raised by a factor of 7 for the estimate based on rat data and 12 for the estimate based on mice. The use of an upper 95 percent confidence limit for the linearized multistage model utilized in the low-dose extrapolation probably overestimates the risk for rodents. Assuming equal susceptibility for rodents and humans, and also using the most tumor-sensitive site

and species, in conjunction with conservative estimates of exposure, also probably overestimate the risks for humans.

H. The Panel's Conclusion

The panel stated in its conclusion that studies have been conducted on TLC separated dyes that showed that impurities in the color additives (UV-absorbing) were mutagenic by the Ames test while the purified dye fraction had little indication of mutagenicity. The panel concluded that the levels of these impurities (i.e., because the levels may vary from one batch of the color additive to another) may have an impact on D&C Red No. 19 carcinogenicity. However, the panel found that because of the relatively low concentration of these impurities, their presence is not likely to alter the risk assessment calculations of risk of the entire dye by a significant degree.

Although the panel characterized the risk of exposure to D&C Red No. 19 as "low," the panel recommended that the impurities be removed before the color additive is used. The panel indicated that it believed it was possible to develop simple, cost-effective techniques for removing impurities which have significant mutagenic action. The panel noted that such a "purification step" would probably reduce the "already small risk" presented by the external uses of D&C Red No. 19.

Finally, the panel noted that the dye has been shown to be phototoxic. The panel suggested that FDA consider prescribing conditions for the use of the dye that would take into account the possibility of effects as a result of light exposure.

XI. FDA's Decision to Permanently List D&C Red No. 19

A. Reliance on Risk Estimation Techniques

The data and information regarding the safety of D&C Red No. 19 support FDA's conclusion that the substance as a whole induces cancer when tested in laboratory animals. The data and information, however, do not support any other finding of toxicity.

In the past, because the data and information show that D&C Red No. 19 is a carcinogen when ingested by rats and mice, FDA in all likelihood would have terminated the provisional listing and denied CTFA's petition for the externally applied uses of D&C Red No. 19 without any further discussion. In the present instance, however, CTFA has presented arguments that this color additive can be regulated for safe use in externally applied drugs and cosmetics. The arguments CTFA has presented are based on the premise that a determination of safety may be based on risk assessment techniques. FDA agrees that risk assessment methods are frequently helpful in evaluating the safety of carcinogenic substances. It was for these reasons that the agency requested the panel to determine whether the data and information available concerning D&C Red No. 19 provided an adequate basis from which to make reliable risk estimations. FDA agrees with the panel that CTFA's risk estimates on the use of D&C Red No. 19 in extremely applied drugs and cosmetics, as modified in the panel's report, represent a reliable upper bound risk and that those risk estimates can be used to evaluate the proposed external uses of D&C Red No. 19. FDA also agrees with the panel's resolution of the agency's concerns regarding the possible toxicity of impurities in the color additive.

B. The Safety of D&C Red No. 19

1. The Carcinogenic Risk Presented

Under section 706(b)(4) of the act (21 U.S.C. 376(b)(4)), the so-called general safety clause of the statute, FDA cannot approve a color additive for a particular use unless the data presented to FDA establish that the color additive is safe for that use. Although what is meant by safe is not explained in the general safety provision, the legislative history of the act makes clear that safety requires proof to a reasonable certainty that no harm will result from the proposed use of an additive. Because D&C Red No. 19 has been shown to be a carcinogen when ingested by laboratory animals, as discussed above, the Delaney Clause (section 706(b)(5)(B)(i) of the act) is applicable. A strictly literal application of the Delaney Clause would prohibit FDA from finding that D&C Red No. 19 is safe and, therefore, prohibit FDA from permanently listing the color for externally applied uses in drugs and cosmetics. However, as seen from CTFA's and the panel's risk estimates, the calculated risk for these uses of D&C Red No. 19 is extremely low. In fact, the level is even lower than that level of risk which the agency accepts in other areas concerning carcinogens; for example, its procedures and criteria for permitting carcinogenic food additive residues in animal tissues under section 512(d)(1)(H) of the act, the DES proviso to the Delaney Clause (21 U.S.C. 360b(d)(1)(H)) (see 50 FR 45530, 45541; October 31, 1985; FDA refers to these procedures and criteria as the sensitivity of the method or SOM procedures). The risk is even lower if the panel's concerns regarding purification of the additive are resolved. With such a negligible risk, there is no gain to the public and the statutory purpose is not implemented or served by an agency action delisting the substance.

2. Resolution of the Panel's Concerns

As discussed above, the panel noted that the impurities in the color additive might be responsible for some of its toxicity. The panel recommended, therefore, that the impurities be removed before the additive is used. The panel stated: "It should be possible to develop simple techniques which are cost-effective, and inclusion of a purification step as a criteria for certification, removing those impurities which have signified mutagenic action, would probably reduce an already small risk."

The agency has traditionally ensured purity of the color additives by batch analysis of manufactured batches. Determination of appropriate manufacturing steps to ensure purity, i.e., the ability to meet certification specifications has been left to the responsibility of the color additive manufacturer. In response to the panel's report, FDA has concluded that utilization of this traditional process will ensure the purity of D&C Red No. 19. Accordingly, the agency is establishing stringent chemical specifications regarding subsidiary color, chemical intermediates, and other impurities found in the color additives. The agency has determined the specification limitations for these individual entities by considering the levels found in the toxicological samples and recently certified batches. In each case, the agency has selected a lower value to be established as the specification limit for each chemical entity in the color additive. In addition the agency will require that the lakes of the color additive D&C Red No. 19 be manufactured from previously certified batches, i.e., those batches of the straight color additive that have met the new chemical specifications regarding subsidiary colors, chemical intermediates, and other impurities found in the color additives.

The latter requirement is necessary in light of the panel's view, shared by the agency, that impurities in the color additive should be controlled. The requirement

will ensure that the color additive to which the public is exposed is as close as possible to the substance that was tested and found by the agency to be safe. As an alternative to requiring that the lakes of D&C Red No. 19 be made only from certified batches of the straight color additive, the agency considered whether lakes of the color additive could be analyzed to determine the level of impurities. There are numerous difficulties in attempting such an analysis (for a discussion of these difficulties, see the agency's advance notice of proposed rulemaking concerning lakes of color additives (44 FR 36411, 36414, June 22, 1979)). Given these difficulties and the limitations of available chemical analytical methodologies, the agency is requiring that lakes of D&C Red No. 19 be manufactured from a batch of a certified color additive, in order to ensure that safety characteristics substantially correspond to the color that was tested, found safe, and permanently listed by this document.

In its advance notice of proposed rulemaking concerning lakes, the agency announced its intention to propose general regulations concerning the definition of lakes, the safety of lakes, and the specifications for lakes (44 FR 36411, June 22, 1979). In light of that notice, the agency when listing a color additive has in the past generally deferred final action concerning lakes of the color additive. However, because of potential variation in levels of impurities and the limitations of analytical methods described above, the agency believes it is necessary to impose the requirement for use of the certified straight color additive D&C Red No. 19 prior to laking. This will ensure that the color additive to which the consumer is exposed is as similar as possible to that found by the agency to be safe. All remaining issues involving the lakes of D&C Red No. 19 will be addressed in the agency's ongoing rulemaking proceeding announced in the June 22, 1979, notice.

3. Phototoxicity

In the conclusions of its report concerning D&C Red No. 19, the panel stated that "* * * the dye has been shown to be phototoxic." The panel also advised that "[C]onditions of its use and the possibility of effects as a result of light exposure should be considered." As part of its safety evaluation, the agency has reviewed the issue of potential phototoxicity from the use of D&C Red No. 19 in externally applied drugs and cosmetics.

Historically, the phenomenon of phototoxicity of dyes was first described in the early 1900's when it was observed that paramecium were inactivated and killed when irradiated with visible light in the presence of a dye. Later it was shown that phototoxicity in biological systems involves a combined action of visible light, a dye, and oxygen. Generally, the type of photoactive dyes that are at issue here exhibit their biological effects through a photodynamic mechanism, which leads to the formulation of a reactive species of an oxygen molecule capable of reacting with micro- and macroconstituents of the cell resulting in cell damage or death. Therefore, reactive oxygen and not the dye itself is responsible for the biologic effects. It is known that many dyes in the presence of light and oxygen are capable of producing a photodynamic response, including xanthene dyes such as D&C Red No. 19 and eosin.

Most of the studies involving phototoxicity of photodynamic dyes that are described in the scientific literature were performed in a variety of in vitro test systems ranging from bacterial systems to various cell lines. FDA believes that most photodynamically active dyes irradiated in an in vitro system under the proper conditions will inactivate or kill those cells by a photodynamic mechanism.

D&C Red No. 19, in fact, has not been tested for phototoxicity in vivo using laboratory animals. It is

recognized, however, that this color additive, by virtue of its structure, spectral characteristics, and in vitro testing, has the potential of being photodynamically active. Upon review of the data, the panel reached the same conclusions regarding the phototoxicity potential of D&C Red No. 19.

Based on its safety review, the agency believes that the extrapolated risk of eliciting phototoxic responses in humans from the topical application of this color additive is low. A literature review indicates that only a few in vivo studies with photodynamic dyes have been conducted using topically applied dyes in animal models or in clinical situations. The results of these studies, however, are variable and lack reproducibility (Ref. 11). It has been reported that severe lip photodermatitis can occur when eosin, a xanthene dye, comes in contact with oral mucosa, the sensitive lip tissue which lacks the protective barrier associated with the skin on other portions of the body. In contrast, normal skin to which eosin has been applied is reported to be unaffected in the presence of light.

The evaluation of the safety data for the color additive D&C Red No. 19 does not reveal a potential phototoxicity problem from external uses of the additive. In spite of the previous widespread use of this color additive in lipsticks and lip cosmetics, there are no reported phototoxic problems. The lipstick use and other ingested drug and cosmetic uses of D&C Red No. 19 were terminated by a regulation that was published in the Federal Register of February 4, 1983 (48 FR 5262). It is generally acknowledged that lip tissue represents a most sensitive and susceptible skin site for phototoxic effects as compared to the skin covering other portions of the body. Based on the long-term history of use of D&C Red No. 19 in lipsticks and other external cosmetics without any reported phototoxicity complaints from con-

sumers, the agency concludes that D&C Red No. 19 use does not present a phototoxic hazard to humans.

4. Conclusion

The certification requirements discussed above resolve the concerns raised by the panel and further reduce the small risk of cancer presented by the external use of D&C Red No. 19 to some indeterminable level lower than that calculated by the panel. Under these circumstances, FDA concludes that it should not interpret the Delaney Clause to require a ban on this use of D&C Red No. 19. Therefore, FDA has decided to exercise its inherent authority under the *de minimis* doctrine and concludes that the Delaney Clause does not require a ban in the case of the externally applied uses of D&C Red No. 19. Because there are no other safety problems with this use of D&C Red No. 19, FDA finds that the externally applied uses are safe.

C. CTFA's Legal Arguments

In its various submissions concerning D&C Red No. 19, CTFA argued that the applicable statutory authority under the act and judicial precedent authorize FDA to apply a *de minimis* interpretation of the Delaney Clause for a carcinogenic color additive that presents an insignificant risk of cancer. CTFA also argued that the Delaney Clause does not apply to the external uses of D&C Red No. 19 because the tests on D&C Red No. 19 are not appropriate for the evaluation of the substance.

FDA agrees with the former position and in the following section of this notice discusses the applicability of the *de minimis* doctrine to D&C Red No. 19. The agency, however, disagrees with CTFA's latter argument, one that draws heavily on the agency's decision to list the color additive lead acetate (45 FR 72112, October 31, 1980; 46 FR 15500, March 6, 1981). CTFA's studies show that D&C Red No. 19 induces cancer at sites

remote from the alimentary tract, thus indicating that the color additive is systemically absorbed before acting as a carcinogen.

Under these circumstances, in the absence of any metabolic or other data suggesting that ingestion studies are inappropriate, ingestion studies are appropriate as a basis for risk assessment of externally applied uses of a color additive. A color additive that penetrates the skin can be distributed to remote sites in a manner analogous to the distribution that occurs when an ingested color additive enters the circulatory system from the gastrointestinal tract. FDA delayed its decision on the external uses of D&C Red No. 19 to allow the petitioner time to determine whether there is skin penetration by this additive. The study submitted by the petitioner shows that a portion of the radiolabeled material in D&C Red No. 19 used for the percutaneous study did penetrate the skin and thus would enter the circulatory system.

Moreover, FDA's decision concerning lead acetate was based upon the unusual combination of scientific facts, peculiar to the use of lead acetate in hair dyes, which the agency recognized "will rarely, if ever, be presented again in this context" (45 FR 72112, 72115; October 31, 1980). Similar facts do not exist in the case of D&C Red No. 19. For example, a key factor that influenced FDA's judgment that the Delaney Clause just did not apply to lead acetate was the fact that a background level of lead is always present in the blood of humans, a background level much greater than the possible increase in lead burden that would result from the use of lead acetate in hair dyes. There is, of course, no background level of D&C Red No. 19 in humans. The agency believes that the tests on D&C Red No. 19 are appropriate for an evaluation of the substance under the Delaney Clause.

D. The de Minimis Doctrine and Its Applicability to D&C Red No. 19

Two conditions must apply to justify an agency's exercise of its authority to interpret a legal requirement as not requiring action in *de minimis* situations. First, it must be consistent with the legislative design for the agency to find that a situation is trivial and, therefore, one that need not be regulated. *Alabama Power Co.* v. *Costle*, 636 F.2d 333, 360 (DC Cir. 1979). Second, it must be clear that the situation is in fact trivial, and that no real benefit will flow from regulating the particular situation. *Environment Defense Fund* v. *Environmental Protection Agency*, 636 F.2d 1267, 1283-1284 (DC Cir. 1980). Both conditions apply here.

1. The establishment of a *de minimis* exception to the Delaney Clause is consistent with the legislative design.

In *Alabama Power Co.* v. *Costle*, *supra*, the court stated that the implication of *de minimis* authority is consistent with most statutes. The court stated that unless Congress has been extraordinarily rigid, there is likely a basis for an implication of such authority. *Id.* at 360-361. That Congress was not so rigid as to preclude the implication of *de minimis* authority under the Delaney Clause is evidenced both by the stated congressional intent in enacting the Delaney Clause and by the stated purpose of this provision.

The clearest statement of the congressional intent for the Delaney Clause is in the legislative history of the Color Additive Amendments of 1960. The Senate considered that the calculation of risk would permit interpretation of the Delaney Clause to allow approval of color additives producing a negligible risk. This is clear from a colloquy on the Senate floor initiated by Senator Jacob Javits in debate on his motion to reconsider the vote to approve the Color Additive Amendments. Senator Javits, focusing on the Delaney Clause, made the record clear in discussion with Republican leader Senator Dirk-

sen and committee chairman Senator Hill that the Senate had agreed to pass the Color Additive Amendments with the Delaney Clause based upon its understanding that the authority conferred by that clause "should be used and applied within the 'rule of reason.'" 106 Congressional Record 15381 (July 1, 1960).[1] Both Senator Dirksen and Senator Hill agreed that the "rule of reason" was to be applied in interpreting the Delaney Clause. *Id.* On that basis, Senator Javits did not pursue his motion to reconsider.

The term "rule of reason" was taken from a report to the President from the President's Science Advisory Committee and from the Departments of Agriculture and of Health, Education, and Welfare (the predecessor to the Department of Health and Human Services) that analyzed the effect of the Delaney Clause that is applicable to food additives. That report defines the "rule of reason" as meaning that: "Every statute must be interpreted in the light of reason and common understanding to reach the results intended by the legislature." 106 Congressional Record 15380. The report stated its conclusion that "an area of administrative discretion based on the rule of reason is unavoidable if the clause is to be workable." 106 Congressional Record 15381.

This report on implementation of the food additive provision, relied upon by the Senators as illustrating their understanding of the types of circumstances in which the "rule of reason" would appropriately be applied, accurately predicted the advent of the science of risk as-

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[1] More recently, Senator Javits reviewed this discussion. On July 10, 1985, he sent Margaret Heckler, Secretary of the Department of Health and Human Services, a letter stating that his views had not changed since 1960. He stated that it was his continuing understanding that the rule of reason "would dictate that where the danger to the public is negligible in using products with such color additives, then use should not be prohibited." A copy of Senator Javits' letter to Secretary Heckler is included in the record of this rulemaking.

sessment. The report stated that: "From the experience obtained in animal experiments and study of humans who have been exposed to carcinogens in the course of their work the panel believes that the probability of cancer induction from a particular carcinogen in minute doses may be eventually assessed by weighing scientific evidence as it becomes available." 106 Congressional Record 15380-15381.

Thus, the Senate agreed to adopt the color additive Delaney Clause only with the understanding that the clause would be administered with "a rule of reason," premised on the expectation that scientists would be able to determine the "probability of cancer induction." Thus, far from having been "extraordinarily rigid," Congress clearly contemplated that those administering the Delaney Clause would have discretion to implement that provision in a reasonable way.[2]

The purpose of the Delaney Clause in section 706 of the act is, after all, to protect the public from the possibility of increasing cancer risks through the use of color additives. It does not advance this purpose to prohibit uses that present a risk that is, for all practical purposes, zero. Congress recognized this fact in warning FDA not to "go overboard" in applying the Delaney Clause. 106 Congressional Record 15381. Thus, it is not inconsistent with the Delaney Clause to permit some uses of a carcinogenic color additive when those uses are shown to present a potential carcinogenic risk that is so trivial, based on extremely conservative statistical analyses, as to be the functional equivalent of no risk at all.

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[2] This grant of discretion is not inconsistent with the fact that Congress clearly intended to prevent the imposition of a tolerance for a carcinogen. Where the probability of harm is so small as to be of no practical significance, it is reasonable and appropriate to apply the *"de minimis"* concept. And, doing so does not in any way reflect an intent to set a tolerance.

This interpretation of the Delaney Clause finds support in recent case law. In *Monsanto* v. *Kennedy*, 613 F.2d 947 (D.C. Cir. 1979), the court held that not all chemicals that become components of food need be considered food additives. The court stated that FDA has the authority to ignore a chemical that migrates from plastic packaging material into beverages if the amount of the chemical that migrates is *de minimis*. The court made that statement after it had found that some amount of the chemical in question would become a component of food by migration from packaging material—thus undeniably satisfying a literal reading of the statute. The court was "* * * concerned that the Commissioner may have reached his determination in the belief that he was constrained to apply the strictly literal terms of the statute irrespective of the public health and safety considerations * * *." 613 F.2d at 954. Accordingly, the court emphasized that the "latitude inherent in the statutory scheme to avoid literal application of the statutory definition of 'food additive' in those *de minimis* situations that, in the informed judgment of the Commissioner, clearly present no public health or safety concerns." *Id.* Thus, the *Monsanto* decision is important to the agency's present action even though that case involved the definition of "food additive" and not the application of the Delaney Clause, and even though FDA, when it issued the order that was ultimately reviewed by the court, had not made a final determination as to the carcinogenicity of the chemical at issue, acrylonitrile monomer.

The court also held in *Monsanto* that the "*de minimis*" concept, applied to the threshold "food additive" definiiton, could be utilized to allow the marketing of a substance that presents no real public health risk. See 613 F.2d at 955-956. Thus, the court's decision in *Monsanto* has the practical effect of shielding substances that present effectively no carcinogenic risk from the Delaney Clause. Although the court did not explicitly interpret

the Delaney Clause as inapplicable to such substances, the court presumably knew that if a carcinogenic chemical was disregarded as *de minimis* in relation to the food additive definition, the chemical would not be subject to the Delaney Clause, which applies only when that definition is met. Necessarily, therefore, the court regarded this consequence as legally warranted.

Moreover, in *Scott* v. *FDA* 728 F.2d 322, 325 (6th Cir. 1984), the Sixth Circuit upheld the so-called constituents policy, whereby FDA may approve known carcinogens present in color additives as intermediaries or impurities present at levels too low to cause a response using conventional tests. Noting that FDA had determined the public health risk presented by D&C Green No. 5 was negligible, the court reasoned:

> * * * We find this determination by the *Monsanto* court persuasive and relevant to the particular facts of the instant case. We agree with the FDA's conclusion that since it "has discretion to find that low level migration into food of substances in indirect additives is so insignificant as to present no public health or safety concern * * * it can make a similar finding regarding a carcinogenic constituent or impurity that is present in a color additive" 47 FR 24280 (1982).

In addition to the foregoing precedents, the state of scientific knowledge about cancer when the Delaney Clause was passed also supports the implication of *de minimis* authority under the Delaney Clause and the fact that the provision could not possibly have been meant to be "extraordinarily rigid." In 1958, there were only four substances that were known to induce cancer in humans: soot, radiation, tobacco smoke, and *beta*-naphthylamine (Ref. 12). Only 20 years later, scientists had identified 37 human carcinogens and over 500 animal carcinogens (Ref. 12). This growth in knowledge is in part the result of an enormous increase in carcinogenicity testing

in laboratory animals. As testing increases, more and more substances are found to induce cancer at some site in at least some strain or sex of laboratory animal. For example, of the 86 compounds tested by the National Toxicology Program (NTP) and reported between July 1981 and July 1984, 50 percent were determined to induce some carcinogenic effect (Ref. 13). (It should be noted that many of the compounds tested by NTP were, prior to testing, suspected of being carcinogenic.) Furthermore, recent short- and long-term toxicity testing has shown that a large number of substances naturally present in food are carcinogenic (Ref. 14).

With the advent of sensitive chemical analytical methodologies, scientists have been able to find carcinogens throughout the food supply in extremely small quantities. In 1958, the available methodologies were far less sensitive than they are today. For example, as FDA stated in its 1979 SOM proposal, the sensitivity of the methodologies increased during the period between 1958 and 1978 by "between two and five orders of magnitude" (44 FR 17070, 17075; March 20, 1979). This improved sensitivity has allowed the detection of carcinogens in the parts per trillion level so that, as one scientist has reported, "today substances can be routinely measured at concentrations up to a million times less than was possible in 1958" (Ref. 12).

There is no indication that in 1958 Congress foresaw the likelihood that, within less than 30 years after the Delaney Clause was enacted, science would have progressed so far as to be able to document the widespread presence of trace amounts of proven carcinogens in food. There is no indication that Congress anticipated the extent to which substances, then regarded either as absent from foods or as noncarcinogenic on the basis of less adequate technology, would later prove to be carcinogenic. In short, the scientific knowledge about carcinogens was much more limited in 1958 than it is today.

The solution Congress decided upon in 1958 for handling added carcinogens given that state of knowledge, was not extraordinarily rigid, but was entirely reasonable, i.e., a few substances, present at levels then detectable, would be banned; most food would be unaffected.

Under these circumstances, it would not be consistent with the legislative design for FDA, today, to attempt to prohibit all added carcinogens from the food supply provided the risks presented by permitted levels are trivial. Permitting merely a *de minimis* level of risk from such carcinogens is not only sound regulatory policy but is also consistent with the underlying purpose of the Delaney Clause as enacted in 1958—the assurance that the food supply will be free from any meaningful risk of cancer presented by substances added to food.

For all the foregoing reasons, the agency concludes that it is consistent with the Delaney Clause to permit uses of a carcinogenic color additive when those uses are shown to present a carcinogenic risk that is so trivial, based on extremely conservative statistical analyses, as to be the functional equivalent of no risk at all.

2. The risk from the use of D&C Red No. 19 in externally applied cosmetics is, in fact, so trivial as to be effectively no risk.

According to the panel's revised risk estimates, the highest lifetime level of risk presented to the external uses of D&C Red No. 19 is 1 in 9 million, i.e., 1.1×10^{-7}. In all likelihood the risk is much lower. This risk is not an actuarial risk. An actuarial risk is the risk determined by the actual incidence of an event. In contrast, the computed risk is a projection based on certain conservative assumptions that do not understate risk. The assumptions that were relied upon have been stated previously in the document describing the panel's computations. The risk from the use of D&C Red No. 19 in externally applied drugs and cosmetics will not ex-

ceed 1 in 9 million and is likely to be somewhere between some much lower level and zero. The 1 in 9 million level represents a 1 in 9 million increase in risk over the normal risk of cancer in a lifetime. FDA emphasizes that this level of risk does not mean that 1 in every 9 million people will contract cancer as a result. Rather, in all likelihood, no one will contract cancer as a result of this exposure. In addition, the agency is requiring more stringent certification specifications which should lower risks.

In light of the level of risk presented by the external uses of D&C Red No. 19, FDA finds that the uses are safe, that they impose no additional risk of cancer to the public, and that any risk they may present is of no public health consequence. It is in just these circumstances, where there is no meaningful increase in public health protection from applying the strict, literal terms of a legal standard, that the courts have found the *de minimis* doctrine to be applicable. For example, the court in *Monsanto* equated "*de minimis*" with a finding that migration of an indirect food additive is "insignificant" (613 F.2d at 947) in a context where the court clearly recognized that the real question was the toxicity of a particular level of migration.

Furthermore, FDA and other regulatory agencies have, in the past, found higher risks than those presented by D&C Red No. 19 to be permissible. For example, in the ongoing SOM rulemaking proceeding, FDA has proposed that an assay method sufficient to detect a carcinogenic residue posing a calculated upper bound risk of 1 in 1 million is appropriate because such a level imposes no additional risk of cancer to the public (see 44 FR 17070, 17093; March 20, 1979). The agency has concluded that as a result of this use of the 1 in 1 million level of risk as far as can be determined in all probability, no

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one will contract cancer from admittedly carcinogenic residues in edible animal tissue. (See 50 FR 45530, 45541; October 31, 1985.)

In several proceedings involving the agency's policy for carcinogenic impurities in food and color additives, FDA has also found that a risk on the order of a 1 in 1 million lifetime risk is low enough to be considered safe within the meaning of the general safety clause. See, e.g., the administrative record complied in the rulemaking on D&C Green No. 6 (47 FR 14138; April 2, 1982).

Furthermore, in a notice published in the Federal Register of December 18, 1985 (50 FR 51551), the agency proposed that methylene chloride when used to decaffeinate coffee is safe, in light of the fact that the potential risk posed by permitted levels of methylene chloride residues in coffee does not exceed a level of 1 in 1 million. In that notice, the agency also suggested that the lifetime risk for the use of methylene chloride to decaffeniate coffee is *de minimis.*

Other Federal agencies have also used a 1 in 1 million level as a basis for regulatory decisionmaking permitting human exposure to carcinogens (Ref. 15). In fact, they have sometimes made regulatory decisions that have allowed a cancer risk greater than 1 in 1 million. The Occupational Safety and Health Administration (OSHA), for example, has focused its regulatory efforts on risks in the workplace that are much higher than 1 in 1 million lifetime level of risk.

For example, under the Occupational Safety and Health Act (OSH Act) (29 U.S.C. 651 et seq.), OSHA issues health standards for the workplace. Before issuing a standard, OSHA must make a formal showing of "significant risk from exposure." Accordingly, OSHA uses quantitative risk assessment to compare the magnitude of risk presented by the various possible levels of exposure

to a substance before establishing a permissible exposure limit. In the Federal Register of January 14, 1983 (48 FR 1864), OSHA established a new permissible exposure limit for inorganic arsenic after determining the risk of lung cancer death associated with such a level would be 8 cases per 1,000 workers exposed over a working lifetime. The standard was upheld by the Ninth Circuit Court of Appeals in *ASARCO* v. *OSHA*, 746 F.2d 483 (9th Cir. 1984). In a similar action in the Federal Register of June 22, 1984 (49 FR 25734), OSHA published a final rule establishing a new permissible exposure limit for ethylene oxide. The new 1 part per million permissible exposure limit represented a risk of 12 to 23 excess deaths per 10,000 workers exposed over a working lifetime.

The Environmental Protection Agency (EPA) in recent years has also relied upon the 1 in 1 million lifetime level as a reasonable criterion for separating high risk problems from low risk problems presented by the wide ranging environmental contaminants EPA must regulate. In the Federal Register of November 23, 1984 (49 FR 46294), EPA proposed guidelines for carcinogen risk assessment. The proposal outlined a procedure for characterizing substances based on the experimental weight of evidence of carcinogenicity. For those compounds classified as known or probable human carcinogens, EPA set the 1 in 1 million risk level as the "point of departure" for determining what level of a carcinogen may cause concern.

For example, under the Safe Drinking Water Act (42 U.S.C. 300f et seq.), EPA sets drinking water standards that contain maximum contaminant levels for toxicants, including carcinogens. Maximum contaminant levels for carcinogens that have been promulgated or proposed to date by EPA generally fall into lifetime risk ranges of 1 in 10,000 to 1 in 1 million (Ref. 16). Similarly, EPA recently proposed to establish the 1 in 1 million level as

the "point of departure" in determining the level of control for all known and possible carcinogenic constituents compounds resulting from hazardous waste contamination (51 FR 1602, 1635; January 14, 1986). As an alternative, EPA proposed to consider estimates of population in determining the appropriate level of control for each constituent. Thus, if a very large number of people is believed to be potentially exposed to a very potent carcinogenic constituent released from contaminated land disposal units, EPA could decrease the level of risk to as low as 1 in 10 million. If the size of the potentially exposed population is not large, the "point of departure" would remain at the 1 in 1 million level. However, if a small number of people was believed to be exposed to the contaminant, such that the incidence of cancer would be expected to be small from the exposure, EPA would consider increasing the acceptable risk level to 1 in 100,000 or 1 in 10,000.

Although comparisons between the safety decisions made by OSHA and EPA with those made by FDA must be tempered by the fact that the decisions are made under different statutory frameworks, the decisions do support the consensus proposition that a lifetime level of 1 in 1 million presents an extremely small risk.

Furthermore, FDA's conclusion that a 1 in 1 million level represents an insignificant level of risk has not been arrived at hastily. For example, when it first proposed the SOM procedures and criteria on July 19, 1973 (38 FR 19226), the agency stated that an acceptable level of risk for carcinogenic residues in edible animal tissues would be 1 in 100 million. In the Federal Register of February 22, 1977 (42 FR 10412), the agency concluded that the 1 in 100 million level was unnecessarily conservative in light of the numerous conservatisms implicit in risk assessment and because the level provided only a minor incremental increase in the degree of confidence presented by the higher 1 in 1 million level. The agency

concluded that the 1 in 1 million level constituted a risk level that one could properly consider to present an insignificant public health concern (see also 44 FR 17070; March 20, 1979). In the most recent Federal Register document concerning the SOM rulemaking (50 FR 45530; October 31, 1985), the agency explained that it considered raising the level yet another order of magnitude to 1 in 100,000 but chose not to do so. FDA reasoned that in recent years the 1 in 1 million level has become a benchmark in the evaluation of the safety of carcinogenic compounds administered to food-producing animals. Furthermore, the agency stated that there is currently widespread confidence that this level presents an insignificant risk of cancer. This point is underscored by the fact that every comment on the risk level aspect of the 1979 SOM proposal regarded the 1 in 1 million level as insignificant. In making the decision to retain the 1 in 1 million level for purposes of the SOM proceeding, FDA recognized explicitly that there may be a higher level of risk that is more appropriate to characterize as a "no residue" level, but that in light of the current uncertainties that accompany making a decision as to the most appropriate level of risk, the 1 in 1 million level was the most reasonable and defensible choice (50 FR 45542).

The level of risk presented by D&C Red No. 19 is extremely low. In relation to other risks regulated by FDA and other Federal agencies, the risk presented by the external uses of D&C Red No. 19 is, indeed, trivial.

XII. Conclusion

Based on the foregoing, FDA concludes that the risk of cancer presented by the use of D&C Red No. 19 in externally applied drugs and cosmetics, as limited by this action, is so low as to be essentially nonexistent. Given such a low level of risk, FDA has concluded that there is no safety gain to the public if it interpreted the Delaney Clause to require a ban on this use for the color additive.

Therefore, FDA, exercising its inherent authority under the *de minimis* doctrine, concludes that the Delaney Clause does not require a ban in this situation. Because there are no other known safety problems from the use of D&C Red No. 19 for coloring externally applied cosmetics, FDA finds that the color additive is safe under the prescribed conditions of use set forth in the regulation below.

The agency is establishing new chemical specifications for the Part 74 listings that identify the color additive. D&C Red No. 19 more precisely than those currently listed in 21 CFR 82.1319.

In accordance with § 71.15 (21 CFR 71.15), the petition and the documents that FDA considered and relied upon in reaching its decisions to approve the petition are available for inspection at the Center for Food Safety and Applied Nutrition (address above) by appointment with the information contact person listed above. As provided in § 71.15, the agency will delete from the documents any material that are not available for public disclosure before making the documents available for inspection.

The agency has determined under 21 CFR 25.24 (b) (3) (50 FR 16636; April 26, 1985) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Executive Order 12291 and the Regulatory Flexibility Act (Pub. L. 96-354) do not apply to actions of this type.

XIII. References

The following information has been placed on file at the Dockets Management Branch (address above) and is available for review in that office between 9 a.m. and 4 p.m., Monday through Friday. The final toxicity study

reports, the agency's toxicology evaluations of these studies, and other information relied upon by the agency in reaching its decision are also on file at the Dockets Management Branch for public review.

1. Franz, T. J., "Percutaneous Absorption of D&C Red No. 19 Through Human Skin *In Vitro*," February 1983.

2. "Determination of Subsidiary Colors in Various Lots of D&C Red No. 19 by Thin Layer Chromatography," February 1983.

3. "Final Review and Analysis of Scientific Studies and Risk Assessment Supporting the Safety of D&C Red No. 19 for use in External Cosmetics and Drug Products Not Subject to Incidental Ingestion," February 15, 1983.

4. Letter from E. Edward Kavanaugh to Gerad L. McCowin, April 29, 1986.

5. Division of Toxicology Memorandum of Toxicology Data for D&C Red Nos. 19 and 37, April 25, 1973.

6. Bureau of Foods' Cancer Assessment Committee Memorandum of Conference, August 12, 1982.

7. "Coal Tar Hair Dyes," Proposed Warning Statement, 43 FR 1101, 1103; January 6, 1978.

8. Klaassen, C. D., "Absorption, Distribution and Excretion of Toxicants," *in* "Toxicology, The Basic Science of Poisons," Chapter 3, Casarett, L.J., and J. Doull (Eds.), Macmillan Pub. Co. Inc., New York, pp. 26-44, 1975.

9. "Lead Acetate; Listing As a Color Additive in Cosmetics That Color the Hair on the Scalp," 45 FR 72112, October 31, 1980.

10. "Removal of Stay of Regulation for the Listing of Lead Acetate as a Color Additive in Cosmetics That Color the Hair on the Scalp; Confirmation of Effective Date," 46 FR 15500, March 6, 1981.

11. Kligman, A.M., and K.H. Kaidbey, "Human Models for Identification of Photosensitizing Chemicals," *Journal of the National Cancer Institute*, 69:269, 1982.

12. Wilson, R., "Risks Caused by Low Levels of Pollution, "*Yale Journal of Biology and Medicine*, 51:37, 48, 1978.

13. Haseman, J., et al., "Results From 86 Two-Year Carcinogenicity Studies Conducted by the National Toxicology Program," *Journal of Toxicology and Environmental Health*, 14:621, 634, 1984.

14. Ames, B., "Dietary Carcinogens and Anticarcinogens," *Science*, 221:1256, September 23, 1983.

15. Milvy, P., "A General Guideline for Management of Risk from Carcinogens," *Risk Analysis*, 6:69, 1986.

16. Crouch, E., et al., "The Risks of Drinking Water," *Water Resources Research, 19:1359, 1983.*

XIV. Objections

Any person who will be adversely affected by this regulation may at any time on or before September 8, 1986, file with the Dockets Management Branch (address above) written objections thereto. Each objection shall be separately numbered, and each numbered objection shall specify with particularity the provisions of the regulation to which objection is made and the grounds for the objection. Each numbered objection on which a hearing is requested shall specifically so state. Failure to request a hearing for any particular objection shall constitute a waiver of the right to a hearing on that objection. Each numbered objection for which a hearing is requested shall include a detailed description and analysis of the specific factual information intended to be presented in support of the objection in the event that a hearing is held. Failure to include such a description and analysis for any particular objection shall constitute

a waiver of the right to a hearing on the objection. Three copies of all documents shall be submitted and shall be identified with the docket number found in brackets in the heading of this document. Any objections received in response to the regulation may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday. FDA will publish notice of the objections that the agency has received or lack thereof in the Federal Register.

List of Subjects

21 CFR Part 74

Color additives, Cosmetics, Drugs, Medical devices.

21 CFR Part 81

Color additives, Cosmetics, Drugs.

21 CFR Part 82

Color additives, Cosmetics, Drugs.

Therefore, under the Federal Food, Drug, and Cosmetics Act and under authority delegated to the Commissioner of Food and Drugs, Parts 74, 81, and 82 are amended as follows:

PART 74—LISTING OF COLOR ADDITIVES SUBJECT TO CERTIFICATION

1. The authority citation for 21 CFR Part 74 is revised to read as follows:

Authority: Secs. 701, 706, 52 Stat. 1055-1056 as amended, 74 Stat. 399-407 as amended (21 U.S.C. 371, 376); 21 CFR 5.10.

2. By adding new § 74.1319 to read as follows:

§ 74.1319 D&C Red No. 19.

(a) *Identity.* (1) The color additive D&C Red No. 19 is 9-(2-carboxyphenyl)-3,6-bis(diethylamino)-xanthylium chloride (CAS Reg. No. 81-88-9). The color additive is manufactured by heating phthalic anhydride with diethyl-*m*-aminophenol followed by saponification with base. The color is isolated as the chloride by treatment with hydrochloric acid and is further purified and dried.

(2) Color additive mixtures for use in externally applied drugs made with D&C Red No. 19 may contain only those diluents that are suitable and that are listed in Part 73 of this chapter for use in color additive mixtures for coloring externally applied drugs.

(b) *Specifications.* D&C Red No. 19 shall conform to the following specifications and shall be free from impurities other than those named to the extent that such impurities may be avoided by current good manufacturing practice:

Volatile matter (at 135 °C), not more than 5-percent.

Total color, not less than 92 percent.

Water insoluble matter, not more than 0.25 percent.

Diethyl-*m*-aminophenol, not more than 0.1 percent.

o-(2-Hydroxy-4-diethylaminobenzoyl) benzoic acid, not more than 0.25 percent.

Phthalic acid, not more than 0.25 percent.

Triethylrhodamine, not more than 1.0 percent.

Other subsidiary colors, not more than 0.3 percent.

Lead (as Pb), not more than 20 parts per million.

Arsenic (as As), not more than 3 parts per million.

Mercury (as Hg), not more than 1 part per million.

(c) *Uses and restrictions.* The color additive D&C Red No. 19 may be safely used for coloring externally applied drugs in amounts consistent with current good manufacturing practice.

(d) *Labeling.* The label of the color additive and any mixtures prepared therefrom intended solely or in part for coloring purposes shall conform to the requirements of § 70.25 of this chapter.

(e) *Certification.* All batches of D&C Red No. 19 shall be certified in accordance with regulations in Part 80 of this chapter.

3. By adding new § 74.2319 to read as follows:

§ 74.2319 D&C Red No. 19.

(a) *Identity and specifications.* The color additive D&C Red No. 19 shall conform in identity and specifications to the requirements of § 74.1319(a)(1) and (b).

(b) *Uses and restrictions.* The color additive D&C Red No. 19 may be safely used for coloring externally applied cosmetics in amounts consistent with current good manufacturing practice.

(c) *Labeling.* The label of the color additive and any mixtures prepared therefrom intended solely or in part for coloring purposes shall conform to the requirements of § 70.25 of this chapter.

(d) *Certification.* All batches of D&C Red No. 19 shall be certified in accordance with regulations in Part 80 of this chapter.

PART 81—GENERAL SPECIFICATIONS AND GENERAL RESTRICTIONS FOR PROVISIONAL COLOR ADDITIVES FOR USE IN FOODS, DRUGS, AND COSMETICS

4. The authority citation for 21 CFR Part 81 continues to read as follows:

Authority: Secs. 701, 706, 52 Stat. 1055-1056 as amended, 74 Stat. 399-407 as amended (21 U.S.C. 371, 376); Title II, Pub. L. 86-618; sec. 203, 74 Stat. 404-407 (21 U.S.C. 376, note); 21 CFR 5.10.

§ 81.1 [Amended]

5. In § 81.1 *Provisional lists of color additives* by removing the entry for "D&C Red No. 19" in paragraph (b).

§ 81.27 [Amended]

6. In § 81.27 *Conditions of provisional listing* by removing the entry for "D&C Red No. 19" in paragraph (d) introductory text table.

PART 82—LISTING OF CERTIFIED PROVISIONALLY LISTED COLORS AND SPECIFICATIONS

7. The authority citation for 21 CFR Part 82 is revised to read as follows:

Authority: Secs. 701, 706, 52 Stat. 1055-1056 as amended, 74 Stat. 399-407 as amended (21 U.S.C. 371, 376); 21 CFR 5.10.

8. By revising § 82.1319 to read as follows:

§ 82.1319 D&C Red No. 19.

The color additive D&C Red No. 19 shall conform in identity and specifications to the requirements of § 74.1319 (a)(1) and (b) of this chapter. D&C Red No. 19 is restricted to use in externally applied drugs and cosmetics. D&C lakes shall be made only from batches of D&C Red No. 19 previously certified in accordance with

the requirements of § 74.1319(a)(1) and (b) of this chapter.

Dated: July 30, 1986.

Frank E. Young,

Commissioner of Food and Drugs.

APPENDIX D

21 CFR Parts 74, 81, and 82

[Docket Nos. 83C-0102 and 83C-0129]

D&C Orange No. 17 and D&C Red No. 19

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is announcing that it has received objections to the permanent listing of D&C Orange No. 17 and D&C Red No. 19 as color additives for use in externally applied drugs and cosmetics. The objections to these listings were filed under the formal rulemaking provisions of the Federal Food, Drug, and Cosmetics Act. The objections contended that the Delaney Clause prohibits the agency from approving the use of D&C Orange No. 17 and D&C Red No. 19 because the color additives are animal carcinogens. Neither hearings nor stays were requested. FDA has evaluated the objections and is rejecting them. The agency is also establishing new effective dates for these color additive regulations.

EFFECTIVE DATE: New effective date established: October 6, 1986.

FOR FURTHER INFORMATION CONTACT: Gerad L. McCowin, Center for Food Safety and Applied Nutrition (HFF-330), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-472-5676.

SUPPLEMENTARY INFORMATION:

I. Background

In the Federal Register of August 7, 1986, FDA permanently listed D&C Orange No. 17 and D&C Red. No.

19. Those actions responded to petitions filed by the Cosmetic, Toiletry and Fragrance Association, Inc.

A. D&C Orange No. 17

The final rule for D&C Orange No. 17 (51 FR 28331; Docket No. 83C-0102) established 21 CFR 74.1267 and 74.2267, which list D&C Orange No. 17 for use in externally applied drugs and in externally applied cosmetics, respectively. The final rule also amended 21 CFR 81.1(b) and 81.27 by removing the entries for D&C Orange No. 17 from these regulations. The final rule also revised 21 CFR 82.1267 to state that D&C Orange No. 17 shall conform in identity and specifications to the requirements of § 74.1267(a)(1) and (b).

B. D&C Red No. 19

The final rule for D&C Red No. 19 (51 FR 28346; Docket No. 83C-0129) established 21 CFR 74.1319 and 74.2319, which list D&C Red No. 19 for use in externally applied drugs and in externally applied cosmetics, respectively. The final rule also amended §§ 81.1(b) and 81.27 by removing the entries for D&C Red No. 19 from these regulations. The final rule also revised 21 CFR 82.1319 to state that D&C Red No. 19 shall conform in identity and specifications to the requirements of § 74.1319(a)(1) and (b) and D&C lakes shall be made only from batches of D&C Red No. 19 previously certified in accordance with the requirements of § 74.1319(a)(1) and (b).

In the final rules, FDA gave interested persons until September 8, 1986, to file objections. Concurrently with publication of the final rule on August 7, 1986, FDA extended the closing date for the provisional listing of D&C Orange No. 17 and D&C Red No. 19 until October 6, 1986 (51 FR 28363), to provide time for the receipt and evaluation of any objections submitted in response to the final rule for these color additives.

The agency received from the Public Citizen Litigation Group objections to the permanent listing regulations for both D&C Orange No. 17 and D&C Red No. 19. The objections are on file in the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, under the docket numbers found in the heading of this document. FDA also received comments in support of both regulations for the Cosmetic, Toiletry and Fragrance Association, that have also been placed on file under the same docket numbers. No requests for a hearing were received in response to the listing regulations. The objections and the agency's response to them are summarized below.

II. Objections and the Agency's Response

In two letters dated August 21, 1986, the Public Citizens Litigation Group (PCLG) filed separate objections to FDA's final rules of August 7, 1986, permanently listing D&C Orange No. 17 and D&C Red No. 19. However, PCLG also stated in each of the letters that "* * * because our objections do not raise any issue of material fact, we do not request a hearing" in regard to either of the two listings.

PCLG summarized its objections as follows:

> Since the FDA has concluded that Orange No. 17 [and Red No. 19] is an animal carcinogen, the Delaney Clause * * * absolutely and unequivocally prohibits the agency from approving the use of Orange No. 17 [and Red No. 19] as a color additive in foods, drugs or cosmetics.

PCLG concluded:

> * * * the sole basis for our objection is the contention that the Delaney Clause prohibits the approval of color additives which cause cancer in animals. * * * [B]ecause the agency has already rejected our arguments on this issue [*Public Citizen* v. *Department of Health and Human Services*, No.

> 86-5150, which is currently pending in the U.S. Court of Appeals for the District of Columbia Circuit], there is no purpose which can be served by delaying consideration of this objection. Therefore, we urge the agency to rule promptly on this objection * * *, so that the objectors may seek review in the Court of Appeals of the FDA's interpretation of the Delaney Clause.

The agency rejects the narrow legal interpretation of the Color Additive Amendments of 1960 (21 U.S.C. 376) set forth in these objections. The final rules for D&C Orange No. 17 and D&C Red No. 19 discuss fully the bases for the agency's conclusion that, under any reasonable standard, D&C Orange No. 17 and D&C Red No. 19 are safe for use in externally applied drugs and cosmetics and that the Delaney Clause does not bar the permanent listings of these color additives. FDA incorporates by reference herein all scientific, legal, and policy discussions set forth in the preambles to the August 7, 1986, final rules for these two color additives. Further explanation of the agency's position would serve no useful purpose.

The filing of objections served to stay automatically the effective date of September 9, 1986, for the regulations listing D&C Orange No. 17 and D&C Red No. 19. Section 701(e)(2) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 371(e)(2)) states: "Until final action upon such objections is taken by the Secretary * * *, the filing of such objections shall operate to stay the effectiveness of those provisions of the orders to which the objections are made." Section 701(e)(3) of the act further stipulates that "As soon as practicable * * *, the Secretary shall by order act upon such objections and make such order public."

The agency has completed its evaluation of the objections and concludes that a continuation of the stay of the regulations is not warranted in response to the objec-

tions. Additionally, there was no request for a hearing in conjunction with the objections that were submitted.

In the absence of any other objections and requests for a hearing, the agency, therefore, further concludes that this document constitutes final action on the objections received in response to the regulations as prescribed in section 701(e)(2) of the act. Therefore, the agency is acting to end the stay of the regulations by establishing a new effective date of October 6, 1986, for the regulations of August 7, 1986, listing D&C Orange No. 17 and D&C Red No. 19 as color additives for use in externally applied drugs and cosmetics. The regulations of August 7, 1986, listing D&C Orange No. 17 and D&C Red No. 19 also deleted the entries for the color additives under Part 81. Thus, on October 6, 1986, D&C Orange No. 17 and D&C Red No. 19 will be removed as entries in the provisional listing.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 701, 706, 52 Stat. 1055-1056 as amended, 74 Stat. 399-407 as amended (21 U.S.C. 371, 376)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10), notice is given that the objections filed in response to issuance of 21 CFR 74.1267, 74.2267, 74.1319, and 74.2319 that were published on August 7, 1986 (51 FR 28331 and 28346) do not form a basis for further stay of their effectiveness or require amendment of the regulations. Accordingly, all the amendments promulgated thereby become effective October 6, 1986.

Dated: October 1, 1986.

Frank E. Young,

Commissioner of Food and Drugs.

APPENDIX E

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 74, 81, and 82

[Docket No. 83C-0102]

Correction of Listing of D & C Orange No. 17 for Use in Externally Applied Drugs and Cosmetics

AGENCY: Food and Drug Administration.

ACTION. Final rule; clarification to preamble.

SUMMARY: The Food and Drug Administration (FDA) published the permanent listing of D & C Orange No. 17 as a color additive for use in externally applied drugs and cosmetics in the Federal Register of August 7, 1986 (51 FR 28331). FDA concluded, under the intended conditions of use by humans and the trivial carcinogenic risk posed by such use, that this color additive is safe within the meaning of section 706 of the Federal Food, Drug, and Cosmetic Act and is safe within the meaning of that statute. In the Supplementary Information published with that permanent listing explaining FDA's rationale for this conclusion, FDA stated that D & C Orange No. 17 "induces" cancer in laboratory animals when given very high amounts up to the maximum tolerated dose of this substance. This statement reflected FDA's policy, as a matter of the scientific analysis undergirding its regulatory activity as defined by law, that any chemical shown to induce cancer even in only one strain, gender, and species, at one dose in one experiment, is an animal carcinogen. This statement did not represent a conclusion that this substance induces cancer in animals within the meaning of section 706 of the Fed-

eral Food, Drug, and Cosmetic Act. Rather, FDA concludes that D & C Orange No. 17 does not induce cancer in man or animal within the meaning of the Act and is safe for external use.

EFFECTIVE DATE: February 19, 1987.

FOR FURTHER INFORMATION: Gerad L. McCowin, Center for Food Safety and Applied Nutrition (HFF-330), Food and Drug Administration, 200 C Street, SW., Washington, DC 20204, 202-472-5676.

SUPPLEMENTARY INFORMATION:

I. Introduction

On August 7, 1986, FDA published the permanent listing of D & C Orange No. 17 as a color additive for use in externally applied drugs and cosmetics (51 FR 28331, August 7, 1986). In the preamble to that Final Rule, FDA reviewed a range of scientific studies and arguments presented by several parties. FDA recounted the development of new sensitive analytical methodologies allowing scientists to determine that many substances present in the food supply are carcinogens and to detect known carcinogens in extremely small quantities. Pursuant to its responsibilities under the Federal Food, Drug, and Cosmetic Act to approve food, drug and color additives as safe, FDA is obliged to assure that its regulatory judgment is informed by the most up-to-date scientific methodologies and analytical techniques. Applying such methodologies to the proposed external uses of D & C Orange No. 17, especially quantitative risk assessment, FDA concluded that this substance, for these uses, poses no genuine risk of cancer, and therefore did not induce cancer *within the meaning of section 706(b)(5)(B) of the Act*, the Delaney Clause.

After summarizing the animal toxicity studies for this color additive as part of its explanation of this conclu-

sion, FDA observed that the "data and information regarding the safety of D & C Orange No. 17 support FDA's conclusion that the substance induces cancer when tested in laboratory animals." (51 FR 28341, August 7, 1986). This clarification of the Final Rule is being published to make clear that FDA was not, by this observation, concluding that this additive induces cancer in animals within the meaning of the Delaney Clause. As explained in the permanent listing document (51 FR 28338-41, August 7, 1986), in calculating the risk to man presented by the expected use of D & C Orange No. 17, FDA concluded that absorption of the color additive through the human skin was essentially the same as oral exposure in the rat. By virtue of this essentially one-to-one correspondence in absorption between rodent and man, a conclusion for purposes of the Delaney Clause that a substance at a given level poses a *de minimis* risk to humans implicitly includes the conclusion that a *de minimis* level of risk at a comparable level of exposure is presented to animals. Accordingly, D & C Orange No. 17 can not be said to induce cancer in animals, as well as in man, within the meaning of the Delaney Clause. When a substance causes only a *de minimis* level of risk in animals, it cannot be said to induce cancer in animals within the meaning of the Delaney Clause.

II. The Regulatory Judgment of FDA

As explained in the preamble to the Final Rule (51 FR 28341-45, August 7, 1986), the Delaney Clause, at the very least, gives to the Secretary the same ability to exercise judgment in fulfilling his responsibilities under that statute as other regulatory statutes give to other administrative decision-makers. That is, the Secretary can exercise his expert judgment to conclude that an item has such a *de minimis* impact on public health or welfare as to not trigger the regulatory structures set out by Congress.

In more explicit Delaney Clause terms, this means that FDA can conclude that a particular food or color additive poses no more than a *de minimis* risk of cancer to man or animal and that such an additive is, consequently, safe both in fact and within the meaning of the law. The words "induce cancer in man or animal" as used in the Delaney Clause are terms of art intended to convey a regulatory judgment that is something more than a scientific observation that an additive is carcinogenic in laboratory animals. To limit this judgment to such a simple observation would be to arbitrarily exclude from FDA's consideration developing sophisticated testing and analytical methodologies, leaving FDA with only the most primitive techniques for its use in this important endeavor to protect public health. Certainly the language of the Delaney Clause itself cannot be read to mandate such a counterproductive limit on FDA's discharge of its responsibilities. Moreover, nothing in the legislative history indicates that Congress intended to impose such a scientifically anachronistic meaning on the words of the statute, stopping the technological clock and relegating FDA's expert regulatory judgment to outdated analytical tools.

The need for this clarification stems from the failure of the preamble to the Final Rule to rigorously and unambiguously reserve the expression "to induce cancer" to the meaning conveyed by the statutory term of art. In several places, notably the discussion of the carcinogenic effects of this additive in animals, the preamble says that FDA concluded that this additive "induces" cancer, meaning that it has been observed to cause cancer in test animals when subjected to enormous doses up to the maximum tolerated dose in the laboratory. The use of high doses is, however, the currently accepted method of amplifying exceedingly rare events. Thus, in the laboratory, whether a substance in any way causes cancer may in the first instance be unrelated to the real-world uses of that substance. It is a conclusion reached even if carcinogenic effects are observed "in only one

strain, gender, and species, at one dose in one experiment." However, FDA concluded that this additive was safe for external use, that is, did not "induce" cancer within the meaning of the Delaney Clause, by using quantitative risk assessment to inform its judgment concerning the impact of this additive in real or every day use. This judgment was based on "(1) the amount of color additive applied to the skin and the frequency of application, (2) the concentration of carcinogenic agents in the color additive, (3) the potency of the carcinogenic agents, and (4) the fraction of the applied agents that penetrates the skin." (51 FR 28337, August 7, 1986).

The authority of FDA to approve additives having only a *de minimis* risk of harm is not only a function of the law, but of common, and scientific, sense. As described in the preamble to the Final Rule, "[w]ith the advent of sensitive chemical analytical methodologies, scientists have been able to find carcinogens throughout the food supply in extremely small quantities." (51 FR 28343, August 7, 1986). Consequently, even some human nutrients—such as selenium, chromium, and nickel—when isolated and administered to laboratory animals in the enormous quantities represented by the maximum tolerated dose, have been found to be carcinogenic. In short, without interposing an evaluation of genuine risk of causing cancer, a regulatory assumption that any chemical that has a carcinogenic effect of any kind is unsafe could require that a significant portion of the food supply be banned.

III. Effects of D & C Orange No. 17 on Animals

In the preamble to the Final Rule, FDA explained that D & C Orange No. 17, when used externally, poses a risk to human beings of 1 in 19 billion. At comparable levels of exposure in the rat, D & C Orange No. 17 poses the same level of risk. This level of risk is so remote that it cannot even be said to be a genuine risk at all. This conclusion was a result of a quantitative risk assessment

based, in large part, on a number of animal toxicity studies involving the ingestion of, or exposure to, the additive in quantities so large that the test animals were severely "challenged" but not killed by the high doses (the maximum tolerated dose) of the substance. Such toxicity studies are used to establish whether a substance in fact has any carcinogenic effects, and, if so, the relative strength of the substance's carcinogenicity. Quantitative risk assessment builds on this determination of carcinogenic potency by evaluating the actual danger posed by the substance in the way a human being or animal would be exposed at actual use levels.

Clearly, though D & C Orange No. 17 is carcinogenic when administered in very high doses up to the maximum tolerated dose in animal toxicity studies, those same studies indicate that this additive is not a highly potent carcinogen. Moreover, when real life use is examined, the increased risk of cancer posed by this substance is so trivial as to be nearly meaningless. Similarly, it cannot be said that D & C Orange No. 17 poses anything more than a *de minimis* risk of cancer to animals. Accordingly, FDA has concluded, and clarifies the preamble to the amendments of 21 CFR 74.1267, 81.1, 81.27 and 82.1267 published at 51 FR 28346 on August 7, 1986 to explicitly state, that D & C Orange No. 17 does not induce cancer in man or animal within the meaning of the Delaney Clause. Public Citizen's objections to the permanent listing document of August 7, 1986 are hereby deemed to be applicable to that decision as clarified by this document.

Dated: February 12, 1987.

Frank E. Young,

Commissioner of Food and Drugs.

APPENDIX F

21 CFR Parts 74, 81, and 82

[Docket No. 83C-0129]

Correction of Listing of D & C Red No. 19 for Use in Externally Applied Drugs and Cosmetics

AGENCY: Food and Drug Administration.

ACTION: Final rule; clarification to preamble.

SUMMARY: The Food and Drug Administration (FDA) published the permanent listing of D & C Red No. 19 as a color additive for use in externally applied drugs and cosmetics in the Federal Register of August 7, 1986 (51 FR 28346). FDA concluded, under the intended conditions of use by humans and the trivial carcinogenic risk posed by such use, that this color additive is safe within the meaning of section 706 of the Federal Food, Drug, and Cosmetic Act and is safe within the meaning of that statute. In the Supplementary Information published with that permanent listing explaining FDA's rationale for this conclusion, FDA stated that D & C Red No. 19 "induces" cancer in laboratory animals when given very high amounts up to the maximum tolerated dose of this substance. This statement reflected FDA's policy, as a matter of the scientific analysis undergirding its regulatory activity as defined by law, that any chemical shown to induce cancer even in only one strain, gender, and species, at one dose in one experiment, is an animal carcinogen. This statement did not represent a conclusion that this substance induces cancer in animals within the meaning of section 706 of the Federal Food, Drug, and Cosmetic Act. Rather, FDA concludes that D & C Red No. 19 does not induce cancer in man or animal within the meaning of the Act and is safe for external use.

EFFECTIVE DATE: February 19, 1987.

FOR FURTHER INFORMATION CONTACT: Gerad L. McCowin, Center for Food Safety and Applied Nutrition (HFF-330), Food and Drug Administration, 200 C Street, SW., Washington, DC 20204, 202-472-5676.

SUPPLEMENTARY INFORMATION:

I. Introduction

On August 7, 1986, FDA published the permanent listing of D & C Red No. 19 as a color additive for use in externally applied drugs and cosmetics (51 FR 28346, August 7, 1986). In the preamble to that Final Rule, FDA reviewed a range of scientific studies and arguments presented by several parties. FDA recounted the development of new sensitive analytical methodologies allowing scientists to determine that many substances present in the food supply are carcinogens and to detect known carcinogens in extremely small quantities. Pursuant to its responsibilities under the Federal Food, Drug, and Cosmetic Act to approve food, drug and color additives as safe, FDA is obliged to assure that its regulatory judgment is informed by the most up-to-date scientific methodologies and analytical techniques. Applying such methodologies to the proposed external uses of D & C Red No. 19, especially quantitative risk assessment, FDA concluded that this substance, for these uses, poses no genuine risk of cancer, and therefore did not induce cancer *within the meaning of section 706(b)(5)(B) of the Act*, the Delaney Clause.

After summarizing the animal toxicity studies for this color additive as part of its explanation of this conclusion, FDA observed that the "data and information regarding the safety of D & C Red No. 19 support FDA's conclusion that the substance as a whole induces cancer when tested in laboratory animals." (51 FR 28357, August 7, 1986). This clarification is being published to

make clear that FDA was not, by this observation, concluding that this additive induces cancer in animals within the meaning of the Delaney Clause. As explained in the permanent listing document (51 FR 28354-57, August 7, 1986), in calculating the risk to man presented by the expected use of D & C Red No. 19, FDA concluded that absorption of the color additive through the human skin was essentially the same as oral exposure in the rat. By virtue of this essentially one-to-one correspondence in absorption between rodent and man, a conclusion for purposes of the Delaney Clause that a substance at a given level poses a *de minimis* risk to humans implicitly includes the conclusion that a *de minimis* level of exposure is presented to animals. Accordingly, D & C Red No. 19 cannot be said to induce cancer in animals, as well as in man, within the meaning of the Delaney Clause. When a substance causes only a *de minimis* level of risk in animals, it cannot be said to induce cancer in animals within the meaning of the Delaney Clause.

II. The Regulatory Judgment of FDA

As explained in the preamble to the Final Rule (51 FR 28359-62, August 7, 1986), the Delaney Clause, at the very least, gives to the Secretary the same ability to exercise judgment in fulfilling his responsibilities under that statute as other regulatory statutes give to other administrative decision-makers. That is, the Secretary can exercise his expert judgment to conclude that an item has such a *de minimis* impact on public health or welfare as to not trigger the regulatory strictures set out by Congress.

In more explicit Delaney Clause terms, this means that FDA can conclude that a particular food or color additive poses no more than a *de minimis* risk of cancer to man or animal and that such an additive is, consequently, safe both in fact and within the meaning of the law. The words "induce cancer in man or animal" as used in

the Delaney Clause are terms of art intended to convey a regulatory judgment that is something different than a scientific observation that an additive is carcinogenic in laboratory animals. To limit this judgment to such a simple observation would be to arbitrarily exclude from FDA's consideration developing sophisticated testing and analytical methodologies, leaving FDA with only the most primitive techniques for its use in this important endeavor to protect public health. Certainly the language of the Delaney Clause itself cannot be read to mandate such a counterproductive limit on FDA's discharge of its responsibilities. Moreover, nothing in the legislative history indicates that Congress intended to impose such a scientific anachronistic meaning on the words of the statute, stopping the technological clock and relegating FDA's expert regulatory judgment to outdated analytical tools.

The need for this clarification stems from the failure of the preamble to the Final Rule to rigorously and unambiguously reserve the expression "to induce cancer" to the meaning conveyed by the statutory term of art. In several places, notably the discussion of the carcinogenic effects of this additive in animals, the preamble says that FDA concluded that this additive "induces" cancer, meaning that it has been observed to cause cancer in test animals when subjected to enormous doses up to the maximum tolerated dose in the laboratory. The use of high doses is, however, the currently accepted method of amplifying excedingly rare events. Thus, in the laboratory, whether a substance in any way causes cancer may in the first instance be unrelated to the real-world uses of that substance. It is a conclusion reached even if carcinogenic effects are observed "in only one strain, gender, and species, at one dose in one experiment." However, FDA concluded that this additive was safe for external use, that is, did not "induce" cancer within the meaning of the Delaney Clause, by using quantitative risk assessment to inform its judgment concerning the

impact of this additive in real or everyday use. This judgment was based on "(1) the amount of color additive applied to the skin and the frequency of application, (2) the concentration of carcinogenic agents in the color additive, (3) the potency of the carcinogenic agents, and (4) the fraction of the applied agents that penetrates the skin." (51 FR 28352, August 7, 1986).

The authority of FDA to approve additives having only a *de minimis* risk of harm is not only a function of the law, but of common, and scientific, sense. As described in the preamble to the Final Rule, "[w]ith the advent of sensitive chemical analytical methodologies, scientists have been able to find carcinogens throughout the food supply in extremely small quantities." (51 FR 28360, August 7, 1986).

Consequently, even some human nutrients—such as selenium, chromium, and nickel—when isolated and administered to laboratory animals in the enormous quantities represented by the maximum tolerated dose, have been found to be carcinogenic. In short, without interposing an evaluation of genuine risk of causing cancer, a regulatory assumption that any chemical that has a carcinogenic effect of any kind is unsafe could require that a significant portion of the food supply be banned.

III. Effects of D & C Red No. 19 on Animals

In the preamble to the Final Rule, FDA explained that D & C Red No. 19, when used externally, poses a risk to human beings of 1 in 9 million. At comparable levels of exposure in the rat, D & C Red No. 19 poses the same level of risk. This level of risk is so remote that it cannot even be said to be a genuine risk at all. This conclusion was a result of a quantitative risk assessment based, in large part, on a number of animal toxicity studies involving the ingestion of, or exposure to, the additive in quantities so large that the test animals were severely "challenged" but not killed by the high doses (the

maximum tolerated dose) of the substance. Such toxicity studies are used to establish whether a substance in fact has any carcinogenic effects, and, if so, the relative strength of the substance's carcinogenicity. Quantitative risk assessment builds on this determination of carcinogenic potency by evaluating the actual danger posed by the substance in the way a human being or animal would be exposed at actual use levels.

Clearly, though D & C Red No. 19 is carcinogenic when administered in very high doses up to the maximum tolerated dose in animal toxicity studies, those same studies indicate that this additive is not a potent carcinogen. Moreover, when real life use is examined, the increased risk of cancer posed by this substance is so trivial as to be nearly meaningless. Similarly, it cannot be said that D & C Red No. 19 poses anything more than a *de minimis* risk of cancer to animals. Accordingly, FDA has concluded, and clarifies the preamble to the amendments of 21 CFR 74.1267, 74.2267, 81.1, 81.27 and 82.1267 published at 51 FR 28346 on August 7, 1986 to explicitly state, that D & C Red No. 19 does not induce cancer in man or animal within the meaning of the Delaney Clause. Public Citizen's objections to the permanent listing document of August 7, 1986 are hereby deemed to be applicable to that decision as clarified by this document.

Dated: February 12, 1987.

Frank E. Young,

Commissioner of Food and Drugs.

APPENDIX G

UNITED STATES COURT OF APPEALS FOR THE DISTRICT OF COLUMBIA CIRCUIT

No. 86-1548

PUBLIC CITIZEN, *et al.*,
Petitioners

v.

DR. FRANK YOUNG, COMMISSIONER,
FOOD AND DRUG ADMINISTRATION, *et al.*,
Respondents

COSMETIC, TOILETRY AND FRAGRANCE ASSOCIATION,
Intervenor

[Filed Oct. 23, 1987]

PETITION FOR REVIEW OF AN ORDER OF THE FOOD AND DRUG ADMINISTRATION

Before: RUTH B. GINSBURG and WILLIAMS, *Circuit Judges*, and HAROLD H. GREENE,* *District Judge.*

JUDGMENT

This cause came on to be heard on the petition for review of an order of the Food and Drug Administration,

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* Of the United States District Court for the District of Columbia, sitting by designation pursuant to 28 U.S.C. § 292(a).

and was argued by counsel. On consideration thereof, it is

ORDERED and ADJUDGED, by this Court, that this case is remanded for further proceedings consistent with the Opinion for the Court filed herein this date.

Per Curiam

For The Court

/s/ George A. Fisher
GEORGE A. FISHER
Clerk

Date: October 23, 1987

Opinion for the Court filed by Circuit Judge Williams.

APPENDIX H

FEDERAL FOOD, DRUG, AND COSMETIC ACT

LISTING AND CERTIFICATION OF COLOR ADDITIVES FOR FOODS, DRUGS, AND COSMETICS

When Color Additives Deemed Unsafe

SEC. 706. [21 U.S.C. § 376] (a) A color additive shall, with respect to any particular use (for which it is being used or intended to be used or is represented as suitable) in or on food or drugs or devices or cosmetics be deemed unsafe for the purposes of the application of section 402(c), section 501(a)(4), or section 601(e), as the case may be unless—

(1)(A) there is in effect, and such additive and such use are in conformity with, a regulation issued under subsection (b) of this section listing such additive for such use, including any provision of such regulation prescribing the conditions under which such additive may be safely used, and (B) such additive either (i) is from a batch certified, in accordance with regulations issued pursuant to subsection (c), for such use, or (ii) has, with respect to such use, been exempted by the Secretary from the requirement of certification; or

(2) such additive and such use thereof conform to the terms of an exemption which is in effect pursuant to subsection (f) of this section.

While there are in effect regulations under subsections (b) and (c) of this section relating to a color additive or an exemption pursuant to subsection (f) with respect to such additive, an article shall not, by reason of bearing or containing such additive in all respects in accordance with such regulations or such exemption, be considered adulterated within the meaning of clause (1) of section 402(a) if such article is a food, or within the

meaning of section 601(a) if such article is a cosmetic other than a hair dye (as defined in the last sentence of section 601(a)). A color additive for use in or on a device shall be subject to this section only if the color additive comes in direct contact with the body of man or other animals for a significant period of time. The Secretary may by regulation designate the uses of color additives in or on devices which are subject to this section.

Listing of Colors

(b)(1) The Secretary shall, by regulation, provide for separately listing color additives for use in or on food, color additives for use in or on drugs or devices, and color additives for use in or on cosmetics, if and to the extent that such additives are suitable and safe for any such use when employed in accordance with such regulations.

(2)(A) Such regulations may list any color additive for use generally in or on food, or in or on drugs or devices, or in or on cosmetics, if the Secretary finds that such additive is suitable and may safely be employed for such general use.

(B) If the data before the Secretary do not establish that the additive satisfies the requirements for listing such additive on the applicable list pursuant to subparagraph (A) of this paragraph, or if the proposal is for listing such additive for a more limited use or uses, such regulations may list such additive only for any more limited use or uses for which it is suitable and may safely be employed.

(3) Such regulations shall, to the extent deemed necessary by the Secretary to assure the safety of the use or uses for which a particular color additive is listed, prescribe the conditions under which such additive may be safely employed for such use or uses (including, but not limited to, specifications, hereafter in this section referred to as tolerance limitations, as to the maximum

quantity or quantities which may be used or permitted to remain in or on the article or articles in or on which it is used; specifications as to the manner in which such additive may be added to or used in or on such article or articles; and directions or other labeling or packaging requirements for such additive).

(4) The Secretary shall not list a color additive under this section for a proposed use unless the data before him establish that such use, under the conditions of use specified in the regulations, will be safe: *Provided, however,* That a color additive shall be deemed to be suitable and safe for the purpose of listing under this subsection for use generally in or on food, while there is in effect a published finding of the Secretary declaring such substance exempt from the term "food additive" because of its being generally recognized by qualified experts as safe for its intended use, as provided in section 201(s).

(5) (A) In determining, for the purposes of this section, whether a proposed use of a color additive is safe, the Secretary shall consider, among other relevant factors—

(i) the probable consumption of, or other relevant exposure from, the additive and of any substance formed in or on food, drugs or devices, or cosmetics because of the use of the additive;

(ii) the cumulative effect, if any, of such additive in the diet of man or animals, taking into account the same or any chemically or pharmacologically related substance or substances in such diet;

(iii) safety factors which, in the opinion of experts qualified by scientific training and experience to evaluate the safety of color additives for the use or uses for which the additive is proposed to be listed, are generally recognized as appropriate for the use of animal experimentation data; and

(iv) the availability of any needed practicable methods of analysis for determining the identity and quantity of (I) the pure dye and all intermediates and other impurities contained in such color additive, (II) such additive in or on any article of food, drug or devices, or cosmetic, and (III) any substance formed in or on such article because of the use of such additive.

(B) A color additive (i) shall be deemed unsafe, and shall not be listed, for any use which will or may result in ingestion of all or part of such additive, if the additive is found by the Secretary to induce cancer when ingested by man or animal, or if it is found by the Secretary, after tests which are appropriate for the evaluation of the safety of additives for use in food, to induce cancer in man or animal, and (ii) shall be deemed unsafe, and shall not be listed, for any use which will not result in ingestion of any part of such additive, if, after tests which are appropriate for the evaluation of the safety of additives for such use, or after other relevant exposure of man or animal to such additive, it is found by the Secretary to induce cancer in man or animal: *Provided*, That clause (i) of this subparagraph (B) shall not apply with respect to the use of a color additive as an ingredient of feed for animals which are raised for food production, if the Secretary finds that, under the conditions of use and feeding specified in proposed labeling and reasonably certain to be followed in practice, such additive will not adversely affect the animals for which such feed is intended, and that no residue of the additive will be found (by methods of examination prescribed or approved by the Secretary by regulations, which regulations shall not be subject to subsection (d)) in any edible portion of such animals after slaughter or in any food yielded by or derived from the living animal.

(C) (i) In any proceeding for the issuance, amendment, or repeal of a regulation listing a color additive,

whether commenced by a proposal of the Secretary on his own initiative or by a proposal contained in a petition, the petitioner, or any other person who will be adversely affected by such proposal or by the Secretary's order issued in accordance with paragraph (1) of section 701(e) if placed in effect, may request, within the time specified in this subparagraph, that the petition or order thereon, or the Secretary's proposal, be referred to an advisory committee for a report and recommendations with respect to any matter arising under subparagraph (B) of this paragraph, which is involved in such proposal or order and which requires the exercise of scientific judgment. Upon such request, or if the Secretary within such time deems such a referral necessary, the Secretary shall forthwith appoint an advisory committee under subparagraph (D) of this paragraph and shall refer to it, together with all the data before him, such matter arising under subparagraph (B) for study thereof and for a report and recommendations on such matter. A person who has filed a petition or who has requested the referral of a matter to an advisory committee pursuant to this subparagraph (C), as well as representatives of the Department of Health, Education, and Welfare, shall have the right to consult with such advisory committee in connection with the matter referred to it. The request for referral under this subparagraph, or the Secretary's referral on his own initiative, may be made at any time before, or within thirty days after, publication of an order of the Secretary acting upon the petition or proposal.

(ii) Within sixty days after the date of such referral, or within an additional thirty days if the committee deems such additional time necessary, the committee shall, after independent study of the data furnished to it by the Secretary and other data before it, certify to the Secretary a report and recommendations, together with all underlying data and a statement of the reasons or basis for the recommendations. A copy of the foregoing

shall be promptly supplied by the Secretary to any person who has filed a petition, or who has requested such referral to the advisory committee. Within thirty days after such certification, and after giving due consideration to all data then before him, including such report, recommendation, underlying data, and statement, and to any prior order issued by him in connection with such matter, the Secretary shall by order confirm or modify any order therefore issued or, if no such prior order has been issued, shall by order act upon the petition or other proposal.

(iii) Where—

(I) by reason of subparagraph (B) of this paragraph, the Secretary has initiated a proposal to remove from listing a color additive previously listed pursuant to this section; and

(II) a request has been made for referral of such proposal to an advisory committee;

the Secretary may not act by order on such proposal until the advisory committee has made a report and recommendations to him under clause (ii) of this subparagraph and he has considered such recommendations, unless the Secretary finds that emergency conditions exist necessitating the issuance of an order notwithstanding this clause.

(D) The advisory committee referred to in subparagraph (C) of this paragraph shall be composed of experts selected by the National Academy of Sciences, qualified in the subject matter referred to the committee and of adequately diversified professional background, except that in the event of the inability or refusal of the National Academy of Sciences to act, the Secretary shall select the members of the committee. The size of the committee shall be determined by the Secretary. Members of any advisory committee established under this Act, while attending conferences or meetings of their

committees or otherwise serving at the request of the Secretary, shall be entitled to receive compensation at rates to be fixed by the Secretary but at rates not exceeding the daily equivalent of the rate specified at the time of such service for grade GS-18 of the General Schedule, including traveltime; and while away from their homes or regular places of business they may be allowed travel expenses, including per diem in lieu of subsistence, as authorized by section 5703(b) of title 5 of the United States Code for persons in the Government service employed intermittently. The members shall not be subject to any other provisions of law regarding the appointment and compensation of employees of the United States. The Secretary shall furnish the committee with adequate clerical and other assistance, and shall by rules and regulations prescribe the procedure to be followed by the committee.

(6) The Secretary shall not list a color additive under this subsection for a proposed use if the data before him show that such proposed use would promote deception of the consumer in violation of this Act or would otherwise result in misbranding or adulteration within the meaning of this Act.

(7) If, in the judgment of the Secretary, a tolerance limitation is required in order to assure that a proposed use of a color additive will be safe, the Secretary—

(A) shall not list the additive for such use if he finds that the data before him do not establish that such additive, if used within a safe tolerance limitation, would achieve the intended physical or other technical effect; and

(B) shall not fix such tolerance limitation at a level higher than he finds to be reasonably required to accomplish the intended physical or other technical effect.

(8) If, having regard to the aggregate quantity of color additive likely to be consumed in the diet or to be applied to the human body, the Secretary finds that the data before him fail to show that it would be safe and otherwise permissible to list a color additive (or pharmacologically related color additives) of all uses proposed therefor and at the levels of concentration proposed, the Secretary shall, in determining for which use or uses such additive (or such related additives) shall be or remain listed, or how the aggregate allowable safe tolerance for such additive or additives shall be allocated by him among the uses under consideration, take into account, among other relevant factors (and subject to the paramount criterion of safety), (A) the relative marketability of the articles involved as affected by the proposed uses of the color additive (or of such related additives) in or on such articles, and the relative dependence of the industries concerned on such uses; (B) the relative aggregate amounts of such color additive which he estimates would be consumed in the diet or applied to the human body by reason of the various uses and levels of concentration proposed; and (C) the availability, if any, of other color additives suitable and safe for one or more of the uses proposed.

Certification of Colors

(c) The Secretary shall further, by regulation, provide (1) for the certification, with safe diluents or without diluents, of batches of color additives listed pursuant to subsection (b) and conforming to the requirements for such additives established by regulations under such subsection and this subsection, and (2) for exemption from the requirement of certification in the case of any such additive, or any listing or use thereof, for which he finds such requirement not to be necessary in the interest of the protection of the public health: *Provided*, That, with respect to any use in or on food for which a listed color additive is deemed to be safe by reason of

the proviso to paragraph (4) of subsection (b), the requirement of certification shall be deemed not to be necessary in the interest of public health protection.

Procedure for Issuance, Amendment, or Repeal of Regulations

(d) The provisions of section 701 (e), (f), and (g) of this Act shall, subject to the provisions of subparagraph (C) of subsection (b) (5) of this section, apply to and in all respects govern proceedings for the issuance, amendment, or repeal of regulations under subsection (b) or (c) of this section (including judicial review of the Secretary's action in such proceedings) and the admissibility of transcripts of the record of such proceedings in other proceedings, except that—

(1) if the proceeding is commenced by the filing of a petition, notice of the proposal made by the petition shall be published in general terms by the Secretary within thirty days after such filing, and the Secretary's order (required by paragraph (1) of section 701(e)) acting upon such proposal shall, in the absence of prior referral (or request for referral) to an advisory committee, be issued within ninety days after the date of such filing, except that the Secretary may (prior to such ninetieth day) by written notice to the petitioner, extend such ninety-day period to such time (not more than one hundred and eighty days after the date of filing of the petition) as the Secretary deems necessary to enable him to study and investigate the petition;

(2) any report, recommendations, underlying data, and reasons certified to the Secretary by an advisory committee appointed pursuant to subparagraph (D) of subsection (b) (5) of this section, shall be made a part of the record of any hearing if relevant and material, subject to the provisions of section 7(c) of the Administrative Procedure Act (5 U.S.C., sec.

1006(c)). The advisory committee shall designate a member to appear and testify at any such hearing with respect to the report and recommendations of such committee upon request of the Secretary, the petitioner, or the officer conducting the hearing, but this shall not preclude any other member of the advisory committee from appearing and testifying at such hearing;

(3) the Secretary's order after public hearing (acting upon objections filed to an order made prior to hearings) shall be subject to the requirements of section 409(f)(2); and

(4) the scope of judicial review of such order shall be in accordance with the fourth sentence of paragraph (2), and with the provisions of paragraph (3), of section 409(g).

Fees

(e) The admitting to listing and certification of color additives, in accordance with regulations prescribed under this Act, shall be performed only upon payment of such fees, which shall be specified in such regulations, as may be necessary to provide, maintain, and equip an adequate service for such purposes.

Exemptions

(f) The Secretary shall by regulations (issued without regard to subsection (d)) provide for exempting from the requirements of this section any color additive or any specific type of use thereof, and any article of food, or drug or device, or cosmetic bearing or containing such additive, intended solely for investigational use by qualified experts when in his opinion such exemption is consistent with the public health.

NOTE.—Section 201 of the Labor-Federal Security Appropriation Act, 1944 (21 U.S.C. 377), provides that the

Secretary in carrying into effect this Act "is authorized to cooperate with associations and scientific societies in the revision of the United States Pharmacopeia and in the development of methods of analysis and mechanical and physical tests necessary to carry out the work of the Food and Drug Administration."

Effective date of Sec. 706. The Color Additive Amendments to the Federal Food, Drug, and Cosmetic Act took effect on the date of enactment, July 12, 1960, subject to the provisions of sec. 203, title II, of P.L. 86-618 which follows:

Provisional Listings of Commercially Established Colors

(a) (1) The purpose of this section is to make possible, on an interim basis for a reasonable period, through provisional listings, the use of commercially established color additives to the extent consistent with the public health, pending the completion of the scientific investigations needed as a basis for making determinations as to listing of such additives under the basic Act [the Federal Food, Drug, and Cosmetic Act] as amended by this Act. A provisional listing (including a deemed provisional listing) of a color additive under this section for any use shall, unless sooner terminated or expiring under the provisions of this section, expire (A) on the closing date (as defined in paragraph (2) of this subsection) or (B) on the effective date of a listing of such additive for such use under section 706 of the basic Act, whichever date first occurs.

(2) For the purposes of this section, the term "closing date" means (A) the last day of the two and one-half year period beginning on the enactment date or (B), with respect to a particular provisional listing (or deemed provisional listing) of a color additive or use thereof, such later closing date as the Secretary may from time to time establish pursuant to the authority of this paragraph. The Secretary may by regulation, upon

application of an interested person or on his own initiative, from time to time postpone the original closing date with respect to a provisional listing (or deemed provisional listing) under this section of a specified color additive, or of a specific use or uses of such additive, for such period or periods as he finds necessary to carry out the purpose of this section, if in the Secretary's judgment such action is consistent with the objective of carrying to completion in good faith, as soon as reasonably practicable, the scientific investigations necessary for making a determination as to listing such additive, or such specified use or uses thereof, under section 706 of the basic Act. The Secretary may terminate a postponement of the closing date at any time if he finds that such postponement should not have been granted, or that by reason of a change in circumstances the basis for such postponement no longer exists, or that there has been a failure to comply with a requirement for submission of progress reports or with other conditions attached to such postponement.

(b) Subject to the other provisions of this section—

(1) any color additive which on the day preceding the enactment date, was listed and certifiable for any use or uses under section 406(b), 504, or 604, or under the third proviso of section 402(c), of the basic Act, and of which a batch or batches had been certified for such use or uses prior to the enactment date, and

(2) any color additive which was commercially used or sold prior to the enactment date for any use or uses in or on any food, drug, or cosmetic, and which either (A), on the day preceding the enactment date, was not a material within the purview of any of the provisions of the basic Act enumerated in paragraph (1) of this subsection, or (B) is the color additive known as synthetic betacarotene,

shall, beginning on the enactment date, be deemed to be provisionally listed under this section as a color additive for such use or uses.

(c) Upon request of any person, the Secretary, by regulations issued under subsection (d), shall without delay, if on the basis of the data before him he deems such action consistent with the protection of the public health, provisionally list a material as a color additive for any use for which it was listed, and for which a batch or batches of such material had been certified, under section 406(b), 504, or 604 of the basic Act prior to the enactment date, although such color was no longer listed and certifiable for such use under such sections on the day preceding the enactment date. Such provisional listing shall take effect on the date of publication.

(d)(1) The Secretary shall, by regulations issued or amended from time to time under this section—

(A) insofar as practicable promulgate and keep current a list or lists of the color additives, and of the particular uses thereof, which he finds are deemed provisionally listed under subsection (b), and the presence of a color additive on such a list with respect to a particular use shall, in any proceeding under the basic Act, be conclusive evidence that such provisional listing is in effect;

(B) provide for the provisional listing of the color additives and particular uses thereof specified in subsection (c);

(C) provide with respect to particular uses for which color additives are or are deemed to be provisionally listed, such temporary tolerance limitations (including such limitations at zero level) and other conditions of use and labeling or packaging requirements, if any, as in his judgment are necessary to protect the public health pending listing under section 706 of the basic Act;

(D) provide for the certification of batches of such color additives (with or without diluents) for the uses for which they are so listed or deemed to be listed under this section, except that such an additive which is a color additive deemed provisionally listed under subsection (b)(2) of this section shall be deemed exempt from the requirement of such certification while not subject to a tolerance limitation; and

(E) provide for the termination of a provisional listing (or deemed provisional listing) of a color additive or particular use thereof forthwith whenever in his judgment such action is necessary to protect the public health.

(2)(A) Except as provided in subparagraph (C) of this paragraph, regulations under this section shall, from time to time, be issued, amended, or repealed by the Secretary without regard to the requirements of the basic Act, but for the purposes of the application of section 706(e) of the basic Act (relating to fees) and of determining the availability of appropriations of fees (and of advance deposits to cover fees), proceedings, regulations, and certifications under this section shall be deemed to be proceedings, regulations, and certifications under such section 706. Regulations providing for fees (and advance deposits to cover fees), which on the day preceding the enactment date were in effect pursuant to section 706 of the basic Act, shall be deemed to be regulations under such section 706 as amended by this Act, and appropriations of fees (and advance deposits) available for the purposes specified in such section 706 as in effect prior to the enactment date shall be available for the purposes specified in such section 706 as so amended.

(B) If the Secretary, by regulation—

(i) has terminated a provisional listing (or deemed provisional listing) of a color additive or

particular use thereof pursuant to paragraph (1)(E) of this subsection; or

(ii) has, pursuant to paragraph (1)(C) or paragraph (3) of this subsection, initially established or rendered more restrictive a tolerance limitation or other restriction or requirement with respect to a provisional listing (or deemed provisional listing) which listing had become effective prior to such action,

any person adversely affected by such action may, prior to the expiration of the period specified in clause (A) of subsection (a)(2) of this section, file with the Secretary a petition for amendment of such regulation so as to revoke or modify such action of the Secretary, but the filing of such petition shall not operate to stay or suspend the effectiveness of such action. Such petition shall, in accordance with regulations, set forth the proposed amendment and shall contain data (or refer to data which are before the Secretary or of which he will take official notice), which show that the revocation or modification proposed is consistent with the protection of the public health. The Secretary shall, after publishing such proposal and affording all interested persons an opportunity to present their views thereon orally or in writing, act upon such proposal by published order.

(C) Any person adversely affected by an order entered under subparagraph (B) of this paragraph may, within thirty days after its publication file objections thereto with the Secretary, specifying with particularity the provisions of the order deemed objectionable, stating reasonable grounds for such objections, and requesting a public hearing upon such objections. The Secretary shall hold a public hearing on such objections and shall on the basis of the evidence adduced at such hearing, act on such objections by published order. Such order may reinstate a terminated provisional listing, or increase or dispense with a previously established temporary tolerance limita-

iton, or make less restrictive any other limitation established by him under paragraph (1) or (3) of this subsection, only if in his judgment the evidence so adduced shows that such actions will be consistent with the protection of the public health. An order entered under this subparagraph shall be subject to judicial review in accordance with section 701(f) of the basic Act except that the findings and order of the Secretary shall be sustained only if based upon a fair evaluation of the entire record at such hearing. No stay or suspension of such order shall be ordered by the court pending conclusion of such judicial review.

(D) On and after the enactment date, regulations, provisional listings, and certifications (or exemptions from certification) in effect under this section shall, for the purpose of determining whether an article is adulterated or misbranded within the meaning of the basic Act by reason of its being, bearing or containing a color additive, have the same effect as would regulations, listings, and certifications (or exemptions from certification) under section 706 of the basic Act. A regulation, provisional listing or termination thereof, tolerance, limitation, or certification or exemption therefrom, under this section shall not be the basis for any presumption or inference in any proceeding under section 706(b) or (c) of the basic Act.

(3) For the purpose of enabling the Secretary to carry out his functions under paragraphs (1)(A) and (C) of this subsection with respect to color additives deemed provisionally listed, he shall, as soon as practicable after enactment of this Act, afford by public notice a reasonable opportunity to interested persons to submit data relevant thereto. If the data so submitted or otherwise before him do not, in his judgment, establish a reliable basis for including such a color additive or particular use or uses thereof in a list or lists promulgated under paragraph (1)(A), or for determining the prevailing

level or levels of use thereof prior to the enactment date with a view to prescribing a temporary tolerance or tolerances for such use or uses under paragraph (1)(C), the Secretary shall establish a temporary tolerance limitation at zero level for such use or uses until such time as he finds that it would not be inconsistent with the protection of the public health to increase or dispense with such temporary tolerance limitation.